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safe and practical treatment of the postcoronary patient

A basic characteristic of the postcoronary patient, whether or not cholesterol levels are elevated, is his inability to clear fat from his blood stream as rapidly as the normal subject.[1-3] *Figure #1* graphically illustrates this difference in fat-clearing time by comparing atherosclerotic and normal subjects after a fat meal.[3]

"Slow clearers" gradually accumulate an excess of fat in the blood stream over a period of years as each meal adds an additional burden to an already fat-laden serum. As shown in *figure #2,* the blood literally becomes saturated with large fat particles, presenting a dual hazard to the atherosclerotic patient: the long-term danger of deposition of these fats on the vessel walls,[4] and the more immediate risk of high blood fat levels after a particularly heavy meal possibly precipitating acute coronary embarrassment.[5]

In *figure #3,* the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

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References: **1.** Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. **2.** Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. *7*:225 (Apr.) 1959. **3.** Stutman, L. J., and George, M.: Clin. Res. *7*:225 (Apr.) 1959. **4.** Wilkinson, C. F., Jr.: Annals of Int. Med. *45*:674 (Oct.) 1956. **5.** Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. *163*:727 (March 2) 1957. **6.** Fuller, H. L.: Angiology *9*:311 (Oct.) 1958. **7.** Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959. **8.** Fuller, H. L.: Circulation *20*:699 (Oct.) 1959.

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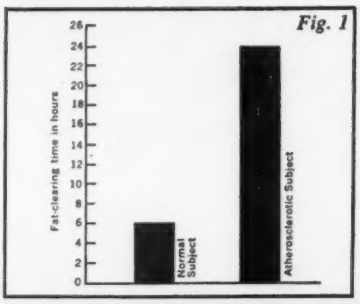

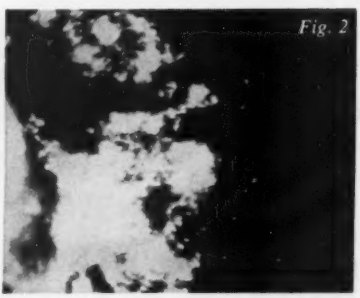

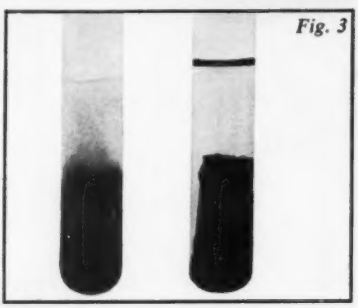

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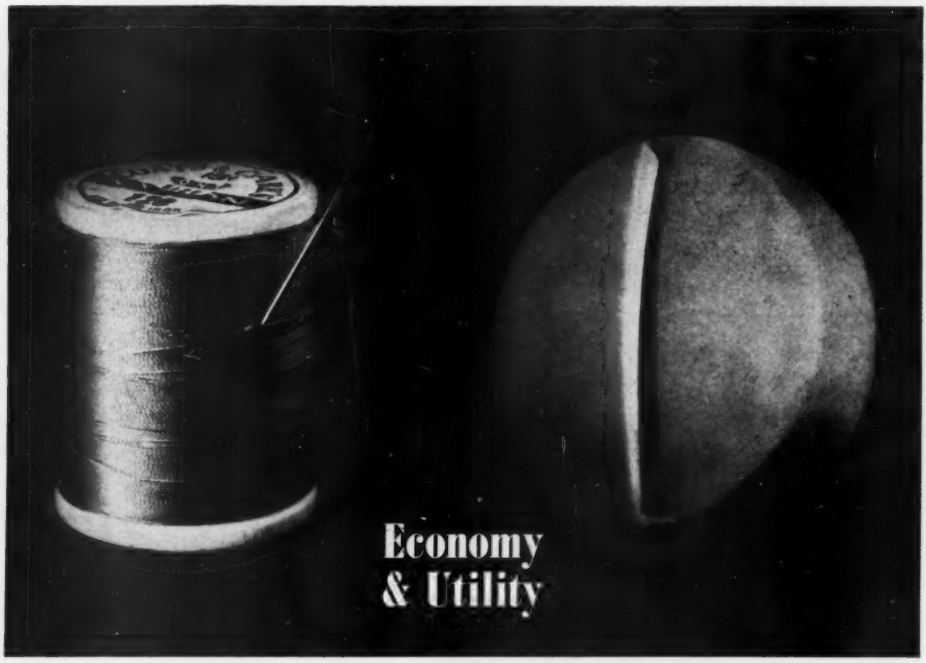

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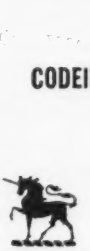

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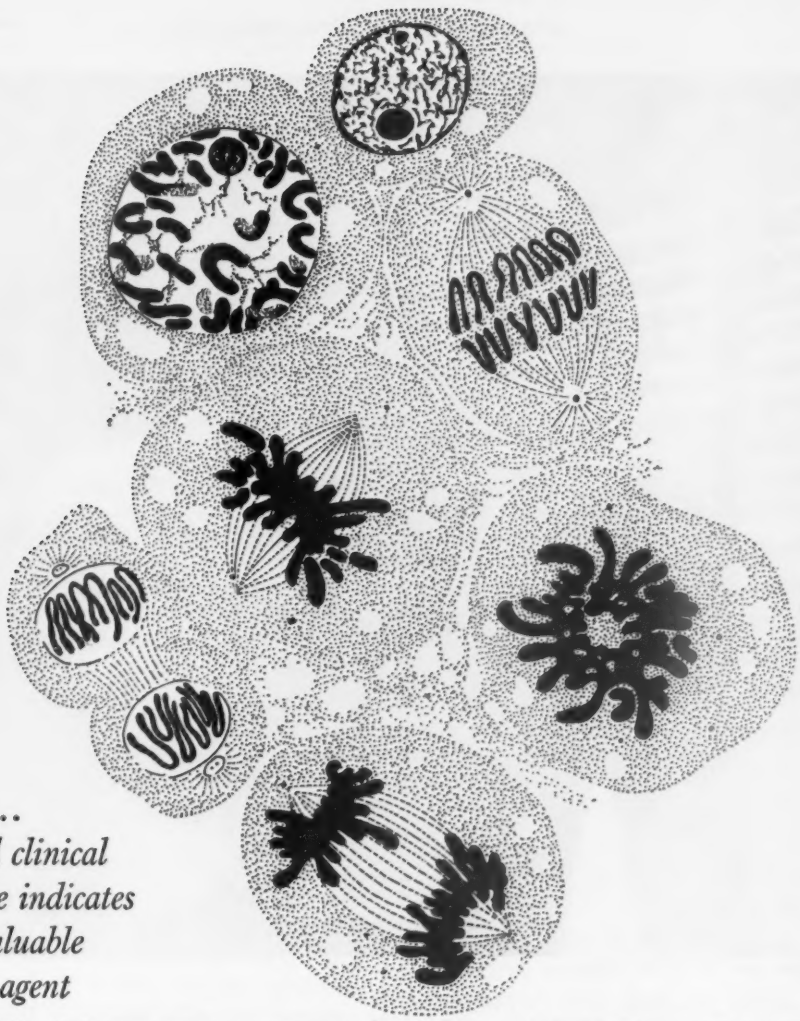

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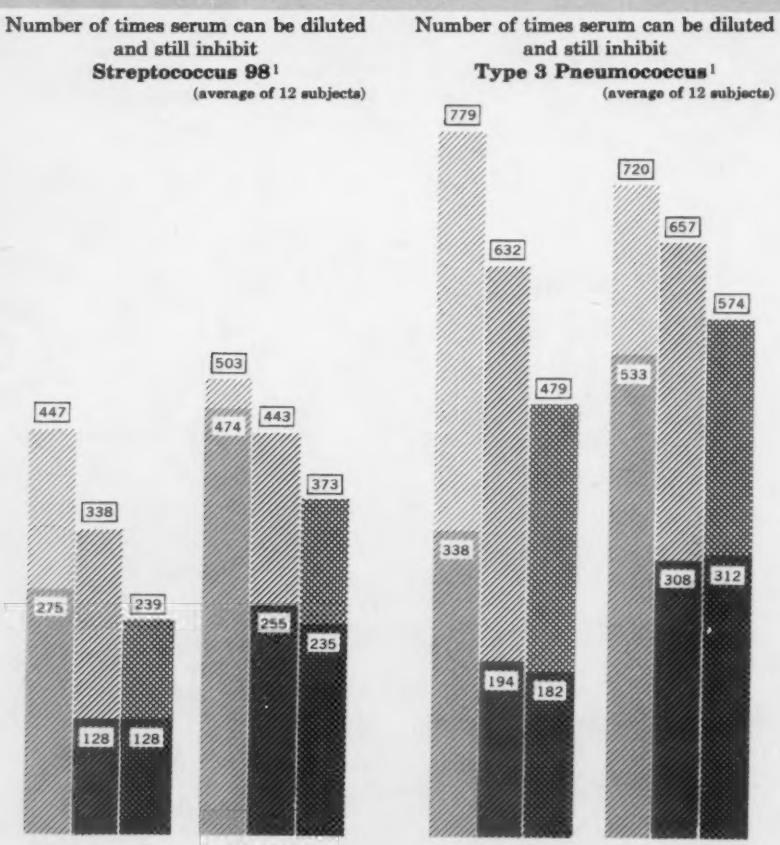
These facts emerge: ➡

Although the concentrations of phenethicillin were higher, "penicillin V [potassium] provided greater activity than phenethicillin against the streptococcus and pneumococcus . . . [and] at least equivalent activity against the staphylococcus. . . ."

—McCarthy, C. G., and Finland, M.: Absorption and Excretion of Four Penicillins, New England J. Med., 263:315 (August 18), 1960.



*Shows "area under the curve," that is, the average of serum dilutions taken over a five-hour period.

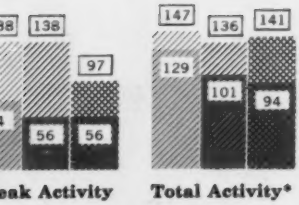
Potassium penicillin V

Phenethicillin (capsules)

Phenethicillin (tablets)

ined areas represent fasting levels;
aded areas depict levels after food.

lumber of times serum can be diluted
and still inhibit
Staphylococcus 209P[1]
(average of 12 subjects)



"Blood Levels" vs. "ABA"

McCarthy and Finland's conclusions extend and confirm their previous observations[2] and those of Griffith.[3] They demonstrate that phenethicillin gives higher "blood levels" in micrograms, but, in terms of antibacterial activity in the serum ("ABA"), potassium penicillin V is clearly superior against the common pathogens (streptococcus and pneumococcus) and at least equal against the staphylococcus.

Furthermore, they show that these high antibacterial levels for potassium penicillin V are less severely affected by food. Thus, whether taken before meals or after, potassium penicillin V provides greater assurance of therapeutic activity.

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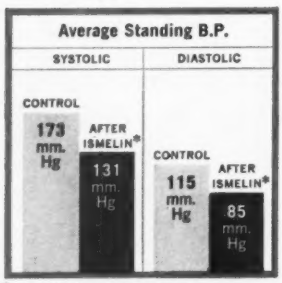
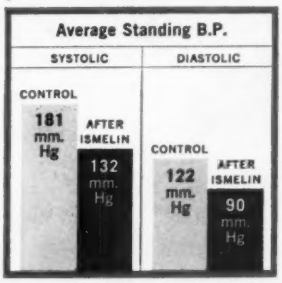
17 of 18 patients (94.4%) treated with Ismelin become normotensive in the erect position. Page and Dustan[1] gave Ismelin orally, alone or in combination with other antihypertensive drugs, to 18 patients daily for 2 to 10 weeks.

RESULTS: All 18 patients had reductions in standing blood pressure; 16 had moderate reductions in supine blood pressure as well. In 17 of the 18 cases, blood pressure levels became normal or near-normal in the erect position.



*During last week of treatment.

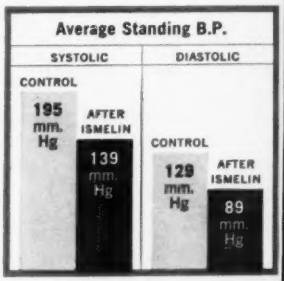
In 14 of 15 patients (93.3%) on Ismelin, blood pressure reduced to normal or near-normal levels in the standing position. Ismelin was administered orally by Frohlich and Freis[2] for 4 to 9 weeks to 15 male patients selected from the hypertensive clinic.



RESULTS: Ismelin evoked a potent antihypertensive response in the erect position: the blood pressure of 14 of the 15 patients dropped to normotensive or near-normotensive levels.

"The response [to Ismelin] was characterized by a potent, orthostatic, antihypertensive effect similar to that seen with the ganglionic blocking drugs but without the side-effects of parasympathetic blockade."[2]

In 15 of 18 subjects (83.3%), guanethidine [Ismelin] reduced high blood pressure to near-normotensive levels. Guanethidine [Ismelin] was administered orally by Richardson and Wyso[3] to 18 male hospitalized patients with hypertension.



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near-normal levels in 80 to 90% of cases[1-3]

RESULTS: "All patients showed definite reduction in blood pressure coincident with administration of [Ismelin]. In most of the subjects [15] standing blood pressure could be maintained near normal levels."[3]

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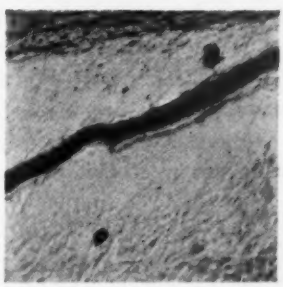

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(Potassium Gluconate, W-T)

READILY ABSORBED

REMARKABLY WELL TOLERATED

EXTREMELY PALATABLE

AVOIDS UNCERTAINTIES OF ENTERIC-COATED TABLETS AND DANGERS OF INTRAVENOUS POTASSIUM

A tablespoonful of KAON Elixir twice daily (30 cc.) supplies the approximate normal daily potassium requirement (40.0 mEq.) — is approximately equal to the elemental potassium in one fourth gallon of orange juice. One teaspoonful (5 cc) approximately equals the potassium in 0.5 Gm. of potassium chloride.

WITH ADRENAL CORTICOID THERAPY, KAON IS USEFUL IN PREVENTING POTASSIUM DEPLETION.

References:

W. J. Kolff, "Acute Renal Failure: Causes and Treatment," The Medical Clinics of North America, *30*:1052 (July 1955).

Peter Forsham, "Symposium on Adrenal Corticoid Therapy," Metabolism, 7:19 (Jan. 1958).

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THE WARREN-TEED PRODUCTS COMPANY

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KEEPS THE STOMACH FREE OF PAIN

tranquilizer

KEEPS THE MIND OFF THE STOMACH

Milpath acts quickly to suppress pain and spasm, and to allay anxiety and tension with minimal side effects.

AVAILABLE IN TWO POTENCIES:

Milpath-400 – Yellow, scored tablets of 400 mg. Miltown (meprobamate) and 25 mg. tridihexethyl chloride. Bottle of 50.

Dosage: 1 tablet t.i.d. at mealtime and 2 at bedtime.

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Milpath®

®Miltown + *anticholinergic*

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1230

in edema or

▪ more doctors are prescribing –
▪ more patients are receiving the benefits of –
▪ more clinical evidence exists for –

in congestive failure

"Chlorothiazide was given to 16 patients for a total of 295 patient-treatment days." "Chlorothiazide is a safe, oral diuretic with a clinical effect equal to or greater than a parenteral mercurial." Harvey, S. D. and DeGraff, A. C.: N. Y. State J. Med., **59**:1769. (May 1) 1959.

in hypertension

". . . our program has been one of polypharmacy in which we attempt to deplete body sodium with chlorothiazide. This drug is continued indefinitely as background medication for all antihypertensive drugs." Moyer, J. H.: Am. J. Cardiology, **3**:199, (Feb.) 1959.

in premenstrual edema

"Chlorothiazide is an excellent agent for relief of swelling and breast soreness associated with the premenstrual tension syndrome, since all patients [50] with these complaints were completely relieved." Keyes, J. W. and Berlacher, F. J.: J.A.M.A., **169**:109, (Jan. 10) 1959.

DOSAGE: Edema—One or two 500 mg. tablets DIURIL once or twice a day. Hypertension—One 250 mg. tablet DIURIL twice a day to one 500 mg. tablet DIURIL three times a day.

SUPPLIED: 250 mg. and 500 mg. scored tablets DIURIL (chlorothiazide) in bottles of 100 and 1,000.

DIURIL is a trademark of Merck & Co., Inc.

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hypertension

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(CHLOROTHIAZIDE)

than for all other diuretic-antihypertensives combined!

in edema of pregnancy

"One hundred patients were treated with oral chlorothiazide." "In the presence of clinically detectable edema, the agent was universally effective." "Chlorothiazide is at present the most effective oral diuretic in pregnancy." Landesman, R., Ollstein, L. N. and Quinton, E. J.: N. Y. State J. Med., **59**:66, (Jan. 1) 1959.

in cirrhosis with ascites

"All three of the patients with Laennec's cirrhosis, ascites and edema had a favorable response, with a mean weight loss of 8 lbs., during the five-day treatment period with a slight decrease in edema." Castle, C. N., Conrad, J. K. and Hecht, H. H.: Arch. Int. Med., **103**:415, (March) 1959.

in renal edema

"In a study of 10 patients with the nephrotic syndrome associated with various types of renal disease, orally administered chlorothiazide was a successful, and sometimes dramatic, diuretic agent." Burch, G. E. and White, M. A., Jr.: Arch. Int. Med., **103**:369, (March) 1959.

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Division of Merck & Co., Inc., Philadelphia 1, Pa.

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This is a completely integrated, easy-to-use mobile instrument for the determination of residual volume or functional residual capacity by the closed circuit helium dilution technique. It provides data for the determination of the following values:

- Functional Residual Capacity
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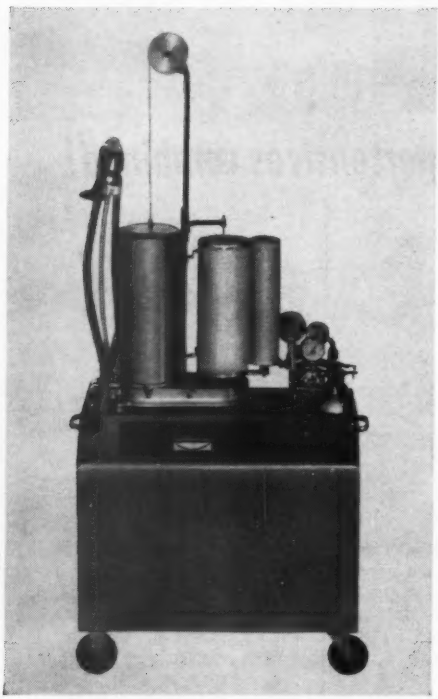

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The Cambridge Pulmonary Function Tester is ideally suited for use in private offices, chest clinics, hospitals and Research Laboratories.

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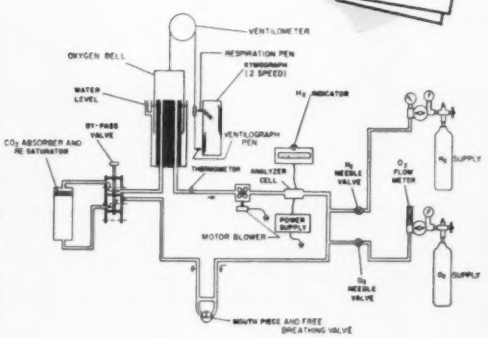

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Graybar Bldg., 420 Lexington Ave., New York 17, N. Y.

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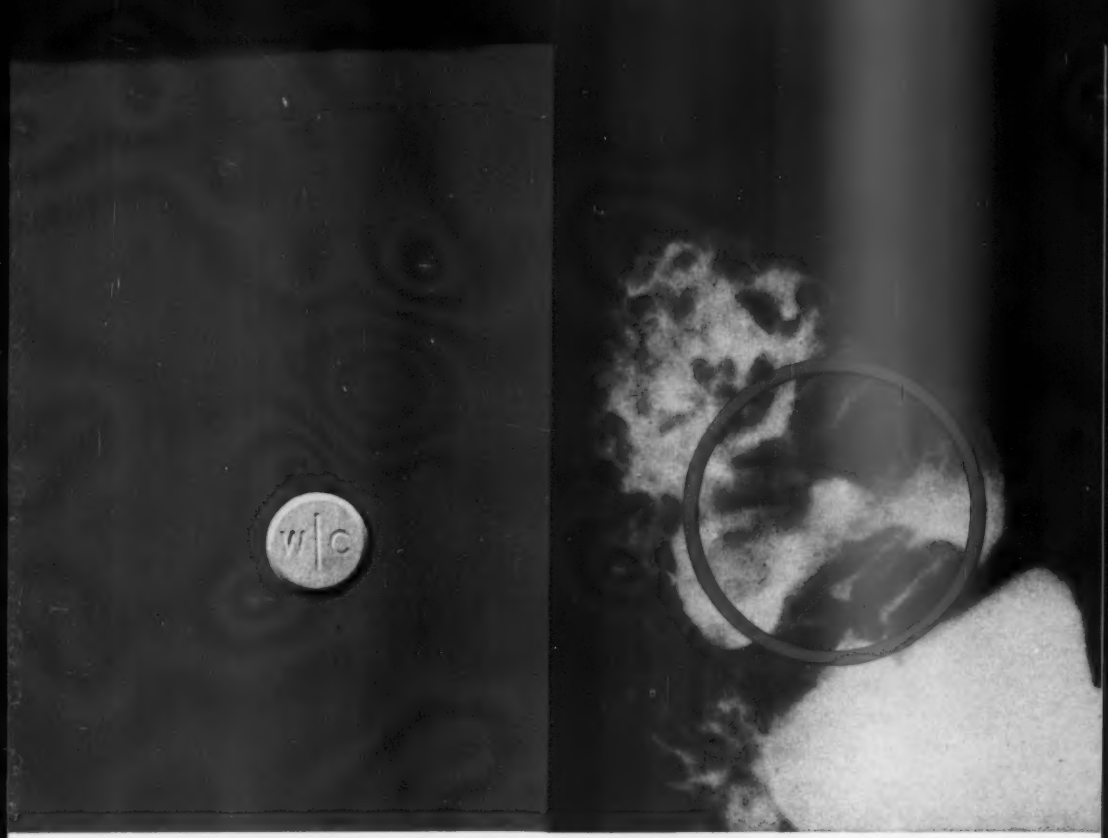

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1. Wharton, G. K. and Osmon, K. L.; Antacid Therapy in Peptic Ulcer: Clin. Med. V:5 (May, 1958).
2. McHardy, G. et al; Exhibit, So. Med. Assn., New Orleans, La., Nov. 1959.

*Full-color photographs with explanatory text of recent photogastroscopy have been mailed to you.

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the physician's antacid

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FOR SIGNIFICANT ANABOLIC GAINS IN: ASTHENIA (UNDERWEIGHT, ANOREXIA, LACK OF VIGOR); CONVALESCENCE FROM SURGERY OR SEVERE INFECTIONS; WASTING DISEASES; BURNS; FRACTURES; OSTEOPOROSIS; AND IN OTHER CATABOLIC STATES

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*Reports to Department of Clinical Investigation, Parke, Davis & Company, 1958 and 1959.

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diuretic-antihypertensive

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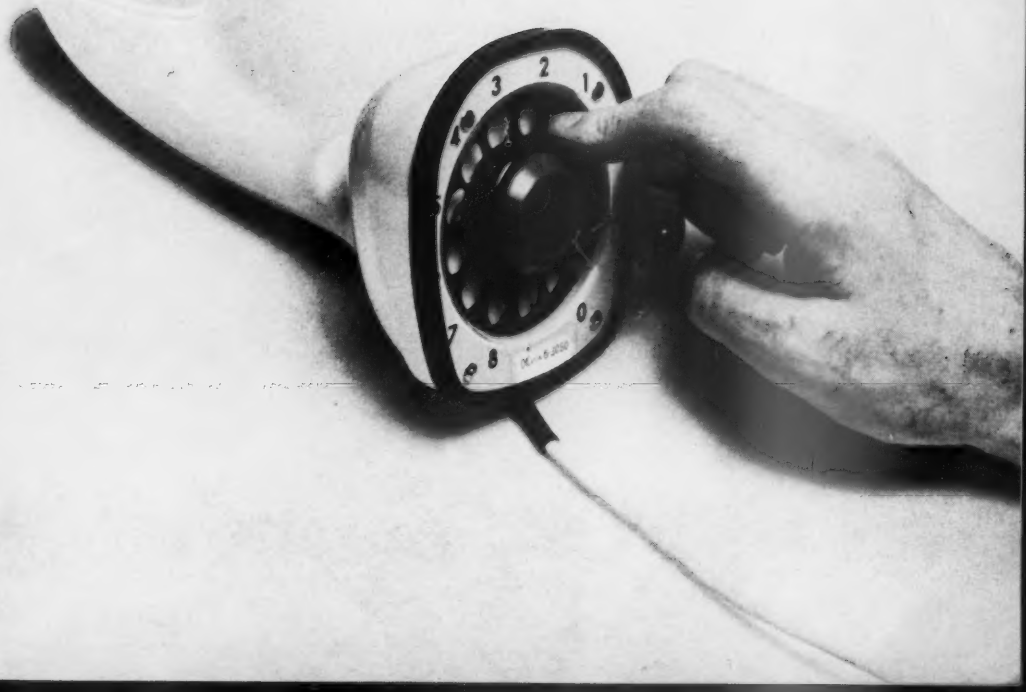
Longest acting of any available thiazide,
more sodium excretion with less potassium loss



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an improved way to treat edema and hypertension

once a day, every day

If you've found the thiazide diuretics helpful, you'll particularly appreciate Enduron. It provides the familiar benefits of oral thiazide therapy, but in a new and (we feel) more practical manner. ■ Dosage, for example, is engineered for the most practical schedule of all: "Once a day, every day." Easy to remember, easy to stick to. ■ More important, *duration* of action of this single daily dose is over 24 full hours. This means your first dose is still producing good diuresis or hypotensive action right up to the time when the next day's dose takes effect. ■ A single dose of 10 mg. produces a peak natruretic effect. By this we mean that the maximum possible effect occurs with 10 mg., and greater doses do not produce greater natruresis. However, most patients require just 5 mg. daily for satisfactory response. Some can be maintained on as little as 2½ mg. Such small doses afford a very safe therapeutic ratio. ■ If you're concerned about potassium, too, you'll like Enduron. It produces the least potassium excretion of any available thiazide. Depletion seldom becomes a factor in your therapy.

See next page for more details . . .

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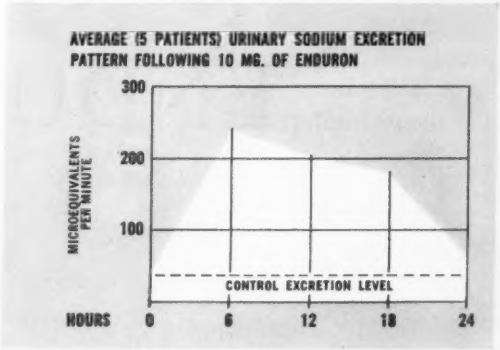
logical culmination to thiazide therapy

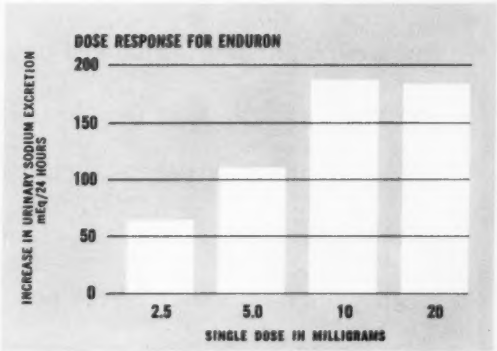
MOST SUSTAINED ACTION OF ANY AVAILABLE THIAZIDE

For once a day dosage to be really satisfactory, it must continue to produce therapeutic effect more than 24 hours later. Otherwise you can expect a gap in action until next day's dose has time enough to re-establish the effect. This gap is avoided with Enduron therapy. Its action remains well above control (i.e., undosed) levels, even at the end of the 24-hour period.



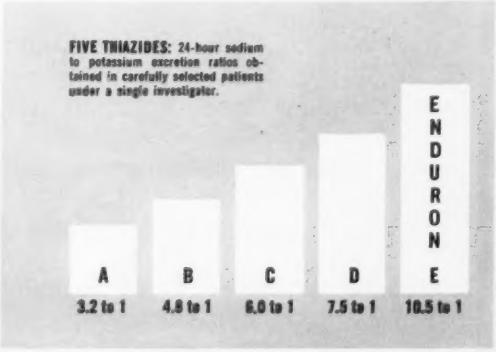
ACHIEVES PEAK NATRURESIS WITH JUST 10 MG.

Enduron is about 20 times more potent than hydrochlorothiazide by weight. It is also more potent compared at peak doses. As explained before, by peak doses we mean the smallest amounts which produce maximum natruretic response. In Enduron that peak is achieved with just 10 mg. (see graph). Larger doses than 10 mg. don't produce additional effect, and aren't needed.



MOST POTASSIUM-SPARING OF ANY AVAILABLE THIAZIDE

Enduron enhances sodium excretion, but doesn't boost potassium outgo proportionately. Its ratio of sodium excretion versus potassium is the most favorable of any available thiazide. In other words, Enduron leads to greater sodium excretion per unit of potassium excreted, and to less total potassium loss than other thiazides. Thus potassium depletion is rarely a problem.



Enduron indications and side reactions are generally comparable to those for the earlier thiazides. Diuresis is prompt, but like other thiazides, several weeks may be required for full hypotensive effect. Enduron has a potentiating action, and you may wish to adjust dosage of other antihypertensive agents if they are used at the same time. Our literature gives full details; ask any Abbott representative or write Abbott Professional Services, North Chicago, Illinois.

Supplied in 2½-mg. (No. 6827) and 5-mg. (No. 6812) square tablets, bottles of 100 and 1000.

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two reliable
oral anticoagulants
adapted to
different needs

Sintrom®
brand of acenocoumarol
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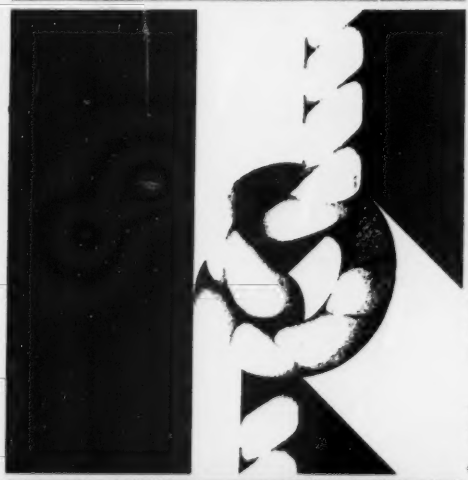

Tromexan is distinguished by rapid onset of hypoprothrombinemic effect and by an equally rapid decline. It is particularly indicated when either prompt anticoagulant effect is imperative or termination of therapy is required, as for surgical intervention.

Sintrom has a rate of action intermediate between that of Tromexan and Dicumarol.® It is noted for the ease with which a stable prothrombin response can be maintained on uniform daily dosage. Consequently it is exceptionally well adapted to long-term therapy.

Tromexan®, brand of ethyl biscoumacetate: Scored tablets of 150 mg. and 300 mg. Sintrom®, brand of acenocoumarol: Double-scored tablets of 4 mg.

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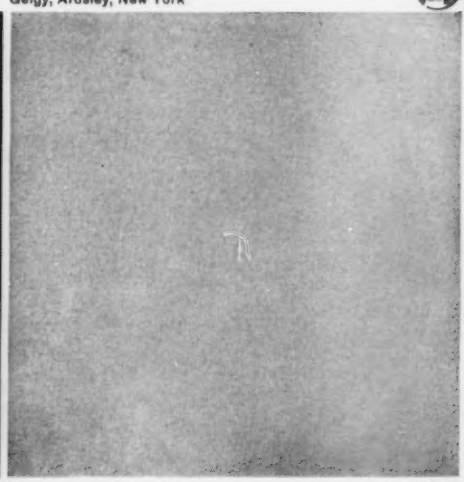
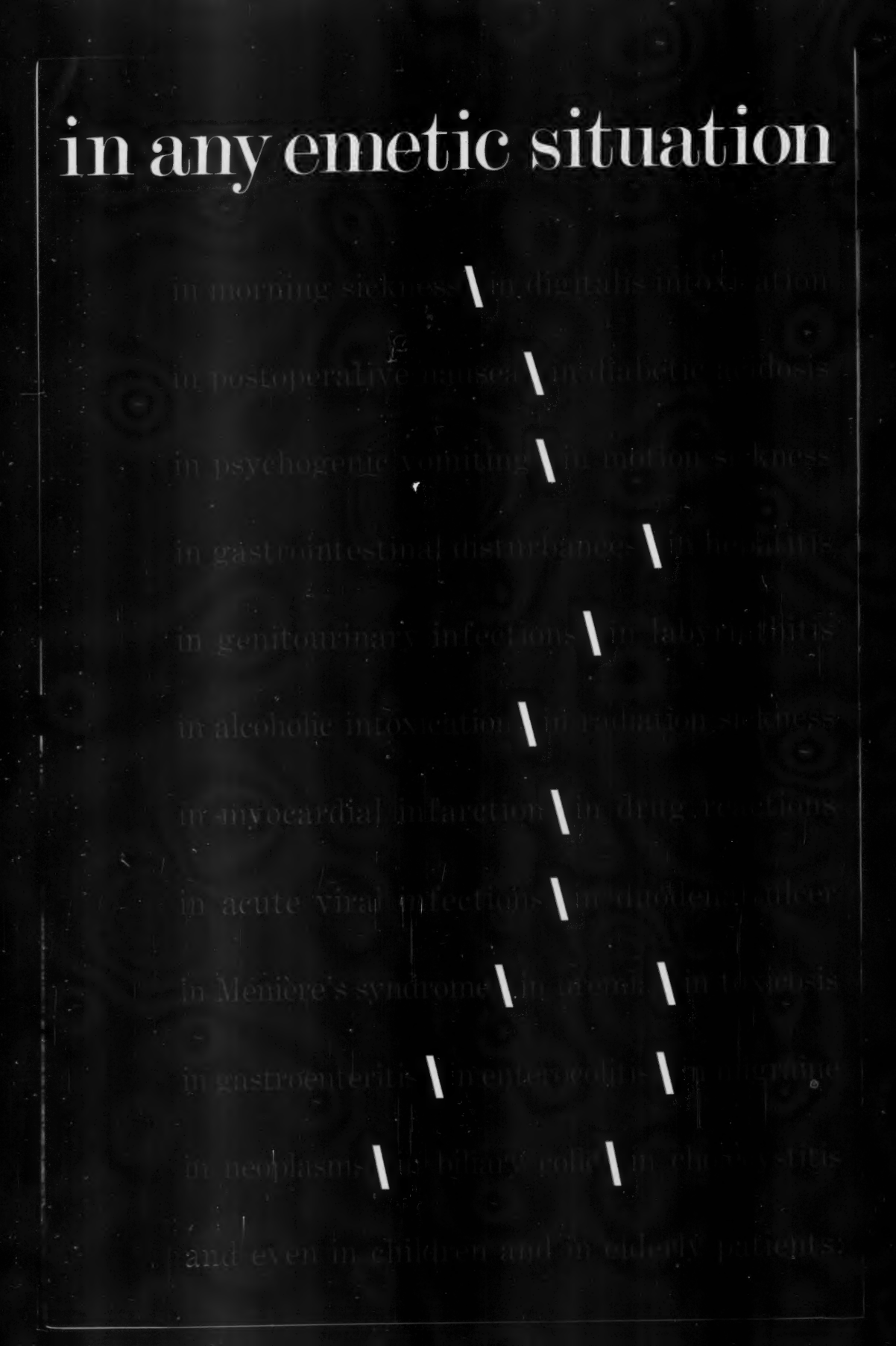


184-60

in any emetic situation



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NEW 250 mg CAPSULES

is safe and sound

Against nausea there's nothing more effective or, for that matter, quite so safe as Tigan. Tigan has *one* demonstrable pharmacologic property: it blocks emetic impulses, primarily by direct action at the chemoreceptor trigger zone (CTZ) of the medulla. Tigan thus *stops* active vomiting as effectively as it prevents nausea and emesis. There are no special precautions, no known contraindications for Tigan. A single chemical compound, Tigan is not a converted antihistamine, tranquilizer or sedative—and may be used even where older antiemetics are contraindicated.

USUAL DOSAGE

ADULTS—*Capsules:* The usual dosage is 100 mg to 250 mg, three or four times daily. In nausea and vomiting of pregnancy, one 250-mg capsule at bedtime and one immediately upon awakening. In severe cases this dose may be repeated up to a total of three or four capsules daily.

Intramuscular Injection: 200 mg (2 cc), one to four times daily.

Suppositories: 200 mg (one suppository), three or four times daily.

CHILDREN—*Capsules:* For children 30 to 90 pounds, one 100-mg capsule, three or four times daily.

Intramuscular Injection: Under 30 pounds, 50 mg (½ cc); 30 to 60 pounds, 100 mg (1 cc); 60 to 90 pounds, 150 mg (1½ cc)—one to four times daily.

Suppositories: Under 30 pounds, 100 mg (½ suppository); 30 to 90 pounds, 100 mg to 200 mg (½ to 1 suppository)—three to four times daily.

NOTE: There are no known contraindications or special precautions to be taken with Tigan therapy. Because Tigan has no sedative or tranquilizer properties, it is *not* necessary for patients to refrain from operating an automobile or other mechanical equipment while on Tigan medication.

Packages: Capsules, blue, 250 mg—bottles of 50. Also available as: 100 mg capsules, blue and white. Ampuls, 2 cc (100 mg/cc). Vials, 20 cc (100 mg/cc). Suppositories, 200 mg.

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In what type of patient is urinary tract infection up to four times more common than in others?

The diabetic. Incidence of infections of the urinary tract in diabetes ranges from 12 to 20 per cent as compared to about 4.5 per cent for the rest of the population.
Source: Peters, B. J.: J. Michigan M. Soc. *57*:1419, 1958.

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"In the presence of urinary infection the determination [of pH] is of the utmost utility. Often therapy is guided as much by the reaction of the urine as by the more detailed bacteriologic studies."[1]

The detection of protein and the detection of sugar in the urine are two of the most commonly performed and diagnostically important tests in all types of medical practice.[2]

NOW... check urine reaction routinely—3 test results in 10 seconds

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Colorimetric combination test for urinary *pH, protein* and *glucose*

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(1) Williamson, P.: Practical Use of the Office Laboratory and X-Ray, Including the Electrocardiograph, St. Louis, C. V. Mosby Company, 1957, p. 41. (2) Free, A. H., and Fonner, D. E.: Studies With a Combination Test for Detection of Glucose and Protein, Abstract of 133rd Meeting, American Chemical Society, San Francisco, April 13-18, 1958, pp. 14c-15c.

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for laxative results without laxative harshness

in chronic constipation **DOXIDAN®** THE SURFACTANT LAXATIVE

Provides positive easy evacuation of a soft, formed, "normal" stool through the synergistic action of the gentle peristaltic stimulant, Danthron, with the superior surfactant, calcium bis-(dioctyl sulfosuccinate). No "griping" or cramping—no bloating—no oily leakage or interference with vitamin absorption.

DOSAGE: For adults and children over 12, one or two capsules. For children, age 6 to 12, one capsule. Administered at bedtime for 2 or 3 days or until bowel movements are normal. Supplied in bottles of 30 and 100 soft gelatin capsules.

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MER/29 *reduces total body cholesterol in 8 out of 10 —and these are the patients most likely to benefit*

your patient with high cholesterol levels...

MER/29 reduces both serum and tissue cholesterol, irrespective of diet.[1] In 463 patients, the mean cholesterol was reduced from 324 mg.% to 253 mg.% — an average decrease of 71 mg.%.[1-6]

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your patient with postmyocardial infarction...

while more time is needed to determine the over-all prognostic significance, it has been observed that MER/29 "...reduced morbidity and mortality rates below those of control series during the first year following coronary thrombosis."[4]

your patient with generalized atherosclerosis...

atherosclerosis "...has been shown to afflict about 77% of American males as early as in the 20-to-30 age range."[9] With MER/29 you have a new, well-tolerated means of lowering cholesterol—considered "...the *sine qua non* of the atheromatous lesion."[9]

compatible with other cardiovascular therapies: MER/29 can be used along with other measures to control anxiety, hypertension, obesity, and other conditions associated with cardiovascular disorders. These include anticoagulants, nitroglycerin, and PETN.

safety data: Patients have now been treated with MER/29 for relatively long and continuous periods. In no case has there been evidence of serious toxic effects on the function of any vital organ or system. However, since long-term MER/29 therapy may be necessary, periodic examinations, including liver function tests, are desirable. Side effects (nausea, headache, dermatitis) are rare and have usually been associated with dosages greater than those recommended for effective therapy.

contraindication: Pregnancy. Since MER/29 inhibits cholesterol biosynthesis, and cholesterol plays an important role in the development of the fetus, the drug should not be administered during pregnancy.

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... the first cholesterol-lowering agent to inhibit the formation of excess cholesterol within the body, reducing both tissue and serum cholesterol

... no demonstrable interference with other vital biochemical processes reported to date

... convenient dosage: one 250 mg. capsule daily before breakfast

... toleration and absence of toxicity established by 2 years of clinical investigation

MER/29

(triparanol)

References: 1. Hollander, W., and Chobanian, A. V.: Boston M. Quart. *10*:37 (June) 1959. 2. Oaks, W., and Lisan, P.: Fed. Proc. *18*:428 (Mar.) 1959. 3. Oaks, W. W., *et al.*: A. M. A. Arch. Int. Med. *104*:527 (Oct.) 1959. 4. Lisan, P.: Proceedings, Conference on MER/29, Progr. Cardiovasc. Dis. *2*:(Suppl.)618 (May) 1960. 5. Oaks, W. W.: *Ibid.*, p. 612. 6. Hollander, W., *et al.*: *Ibid.*, p. 637. 7. Halperin, M. H.: *Ibid.*, p. 631. 8. Toro, J.: *Ibid.*, p. 544. 9. Morrison, L. M.: J.A.M.A. *173*:884 (June 25) 1960.

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in cholecystography . . . minimal PBI interference

For the Radiologist, excellence of visualization and low incidence of side effects[1–10] are two of the many advantages which have recommended Orabilex in cholecystography. **For the Internist,** Orabilex has been shown to cause the least interference with protein bound iodine levels of the commonly used cholecystographic contrast media. **E. Fougera & Company, Inc.**, Hicksville, Long Island, N. Y.

Orabilex* for more rapid return to normal PBI levels

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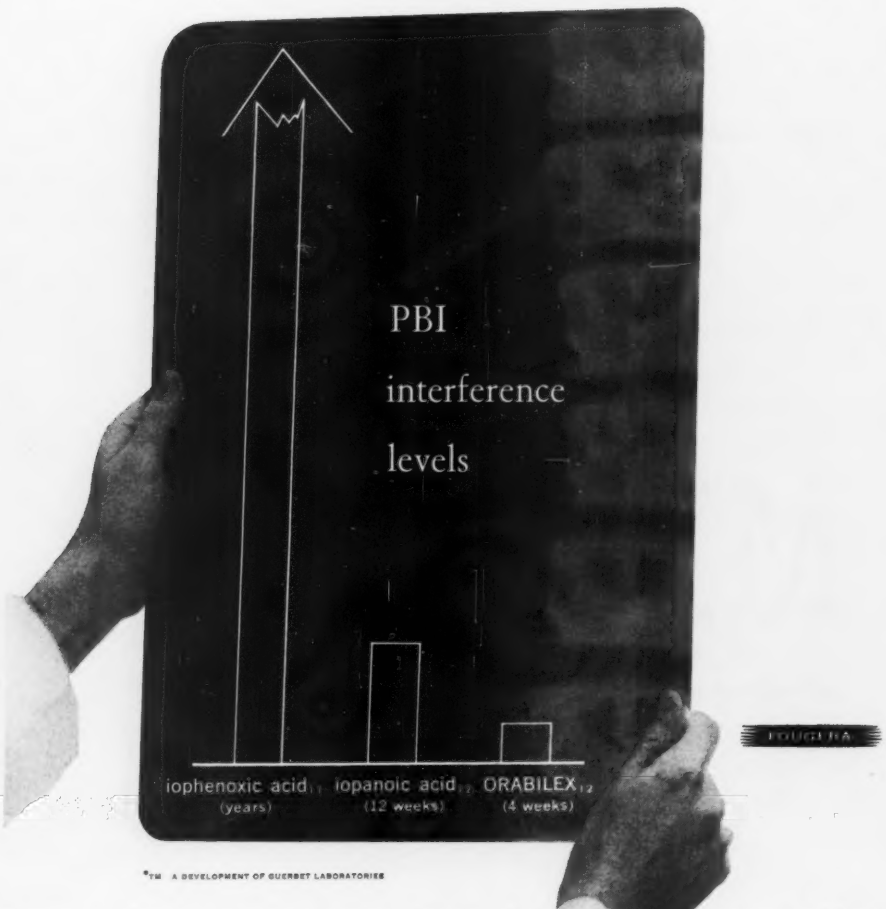

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References: 1. Teplick, J. G. et al: Am. J. Roentgenol. 80:961, Dec. 1958. 2. Tice, G. [illegible] nsas Med. Soc. 60:118, March 1959. 3. Heacock, C. H. & Wilson, J. M.: Memphis M. J. 34:187, May 1959. 4. Whitehouse, W. [illegible] & Fink, H. E., Jr.: Univ. of Michigan M. Bull. 25:238, July 1959. 5. Meszaros, W. T. & Rich, F. M.: J.A.M.A. 172:17, April 23, 1960. 6. Geffen, A.: Radiology 72:839, June 1959. 7. Van Epps, E. F. & Behlke, F. M.: J. Iowa Med. Soc., June 1959. 8. Bickham, C. E. Jr. et al: Southern Med. J. 53:77, Jan. 1960. 9. Morgan, L. A. & Parks, R. E.: Radiology 74:436, March 1960. 10. Reeves, R. J.: Am. J. Roentgenol. 83:5, May 1960. 11. Astwood, E. F.: Tr. Assn. Am. Phys. 70:183, 1957. 12. Shapiro, R. & Man, E. B.: J. A. M. A. 173:12. July 23, 1960.

effectively checking gout

retards the disease
by increasing
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Anturane™
brand of sulfinpyrazone

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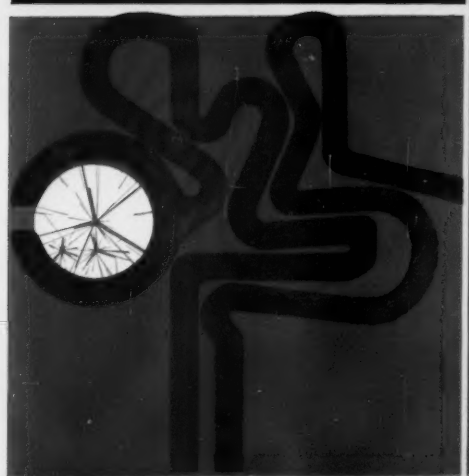

In the treatment of chronic gout, Anturane effectively retards further progression by "draining-off" excess urate, thereby preventing new tophus formation.

The most potent of all uricosuric agents, Anturane enhances urate excretion by an average of 65 per cent ... lowers plasma urate by an average of 30 per cent.[1]

The beneficial results are seen in reduced frequency and severity of acute attacks, relief of interval pain, reduction in joint swelling and improved mobility.[2,3]

1) [illegible] Arch. Rheumat. 2:532, 1958. (2) Kersley, G. D.; Cook, E. W., and Towle, D. C. J.: Ann. Rheumat. Dis. 17:206, 1958. (3) Ogryzlo, M. A., and Harrison, J.: Ann. Rheumat. Dis. 16:428, 1957.

Anturane, brand of sulfinpyrazone: Scored tablets of 100 mg. In bottles of 100.

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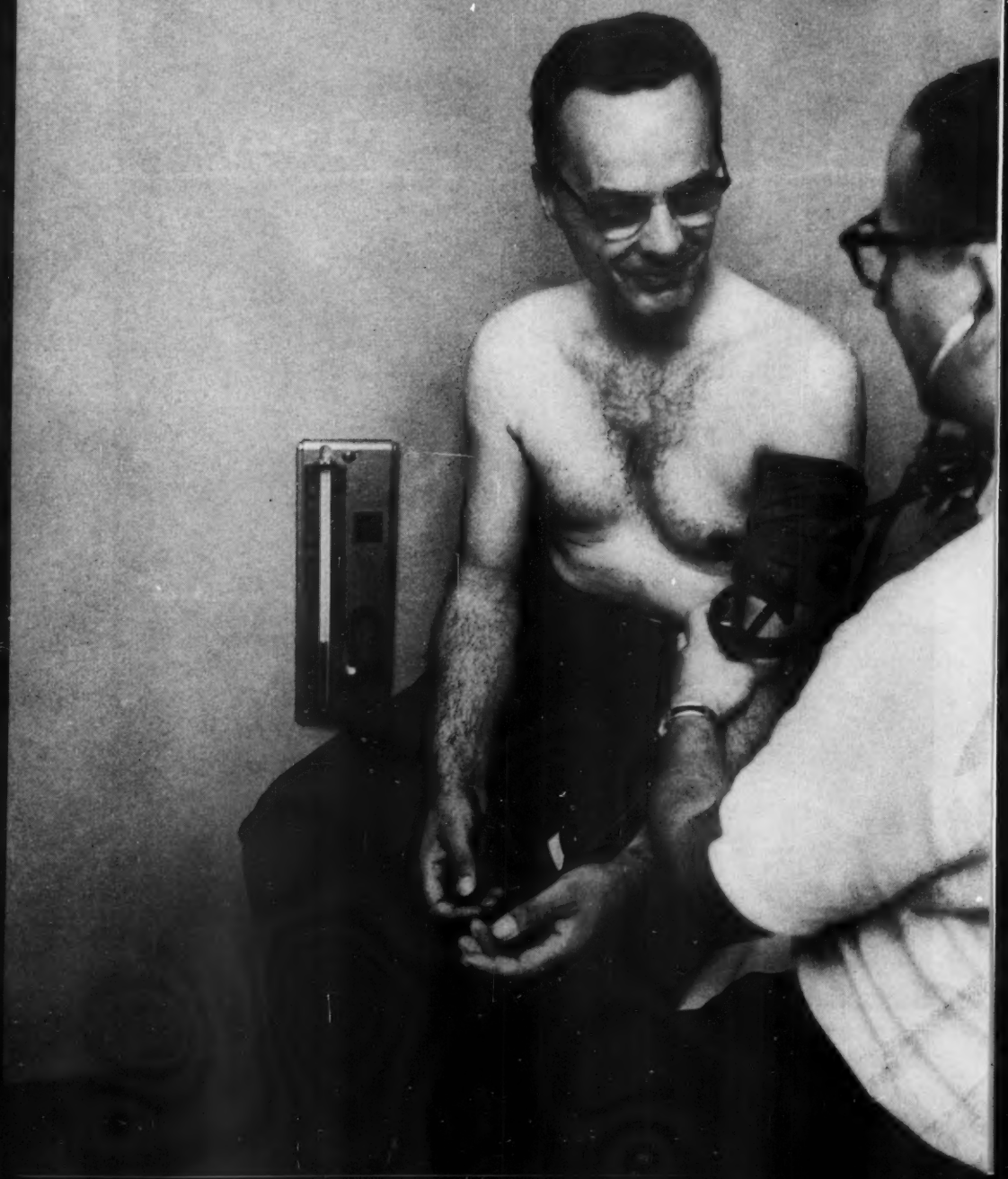
181-60

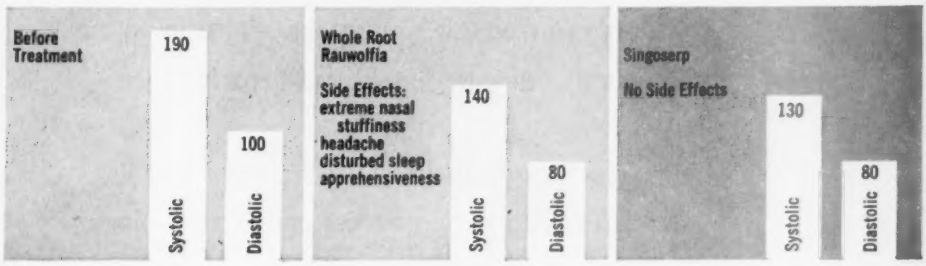
this hypertensive patient prefers Singoserp

Patient's comment: "The other drug [whole root rauwolfia] made me feel lazy. I just didn't feel in the mood to make my calls. My nose used to get stuffed up, too. This new pill [Singoserp] doesn't give me any trouble at all." Photo used with patient's permission.



...and so does his physician

Clinician's report: J.M., a salesman, had a 16-year history of hypertension and was rejected by the U.S. Army because of high blood pressure. When treated with whole root rauwolfia, patient had satisfactory blood pressure response but could not tolerate side effects. Singoserp, in a dose of 0.5 mg. daily, not only reduced patient's blood pressure still further, but did not produce any side effects.



Many hypertensive patients and their physicians prefer Singoserp®

because it usually lowers blood pressure without rauwolfia side effects

SUPPLIED: Singoserp **Tablets,** 1 mg. (white, scored). Also available: Singoserp®-Esidrix® **Tablets** #2 (white), each containing 1 mg. Singoserp and 25 mg. Esidrix; Singoserp®-Esidrix® **Tablets** #1 (white), each containing 0.5 mg. Singoserp and 25 mg. Esidrix. **Complete information sent on request.**

Singoserp® (syrosingopine CIBA)
Singoserp®-Esidrix® (syrosingopine and hydrochlorothiazide CIBA)

2/2845MR

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Positive Antithrombotic Therapy

As you read this, your blood is kept in normal state of flow by endogenous heparin.

When antithrombotic therapy is indicated, LIPO-HEPIN reproduces normal physiologic anticoagulation.

Of increasing importance is the ability of LIPO-HEPIN to alter the physiochemical state of serum lipids, a suspect in the most recent concept of atherosclerotic disease and resulting vascular occlusion.

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heparin sodium, U.S.P., aqueous for intravenous or subcutaneous use

Riker Northridge, California

FOR ASTHMA, EMPHYSEMA, CHRONIC BRONCHITIS

INSPIRED RELIEF IN SECONDS[1]

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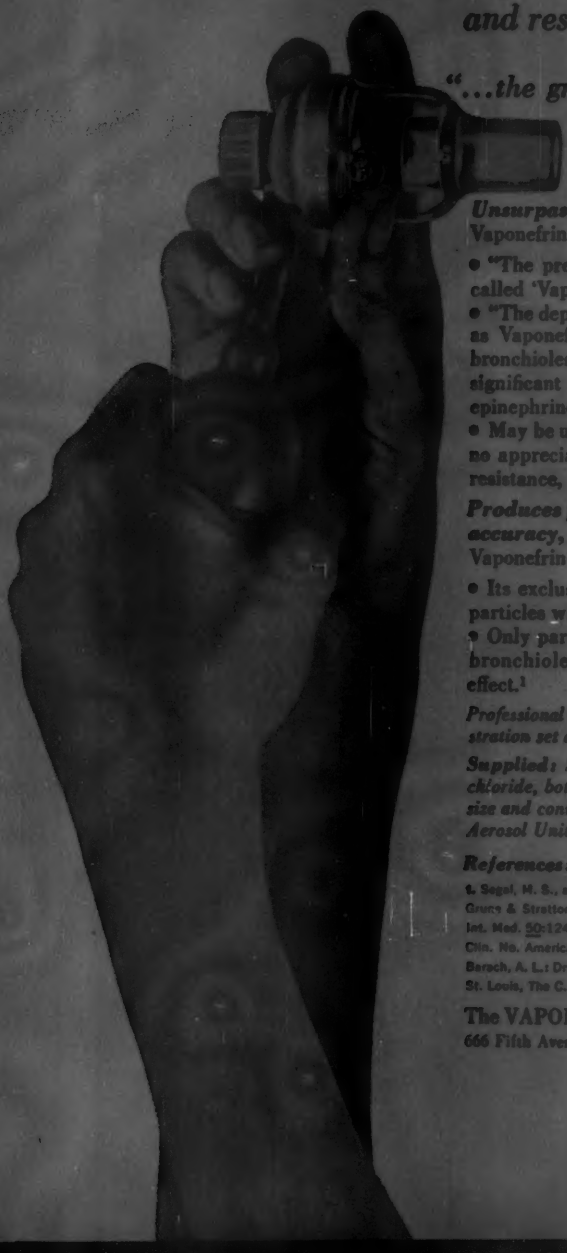
A TEXTBOOK THERAPY FOR ASTHMA

Just 3 to 6 inhalations of Vaponefrin relieve bronchospasm and restore breathing comfort



"...the greatest improvement (in vital capacity-time relationship) occurs during the first second."[1]

Unsurpassed record of efficacy and safety Vaponefrin Solution (racemic epinephrine)...

- "The preparation we have found most effective is called 'Vaponefrin'."[2]
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- May be used by hypertensive and cardiac patients; no appreciable effects on blood pressure, peripheral resistance, C.N.S., with ordinary doses.[3]

Produces particles of critical micrometric accuracy, for maximum efficacy Vaponefrin Nebulizer...

- Its exclusive baffle produces a voluminous mist of particles with average radii of 1 micron.[4]
- Only particles in this range can penetrate smaller bronchioles and alveoli for almost instantaneous effect.[1]

Professional literature and a complimentary office demonstration set available on request.

Supplied: Solution (2.25%) racemic epinephrine hydrochloride, bottles of 7.5, 15 or 30 cc.; Nebulizers, Standard size and conveniently-carried Pocket size. Also Vaponefrin Aerosol Unit (Nebulizer and Solution).

References:

1. Segal, H. S., and Dulfano, M. J.: Chronic Pulmonary Emphysema, New York, Grune & Stratton, 1953, p. 99. 2. Farber, S. M., and Wilson, R. H. L.: Ann. Int. Med. 50:1241, 1959. 3. Barach, A. L., and Cromwell, H. A.: Med. Clin. No. America, May 1940, p. 621. 4. Bickerman, H. A., and Barach, A. L.: Drugs of Choice, 1960-1961 (W. Modell, ed.). St. Louis, The C. V. Mosby Co., 1960, p. 524.

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New, more effective analgesic

Kills pain

stops tension

For neuralgias, dysmenorrhea, upper respiratory distress, and postsurgical conditions...new compound kills pain, stops tension, reduces fever—gives more complete relief than other analgesics.

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NEW NONNARCOTIC ANALGESIC

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Composition: Soma (carisoprodol), 200 mg.; phenacetin, 160 mg.; caffeine, 32 mg. **Dosage:** 1 or 2 tablets q.i.d. **Supplied:** Bottles of 50 apricot-colored, scored tablets.

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BOOSTS THE EFFECTIVENESS OF CODEINE: Soma Compound boosts the effectiveness of codeine. Therefore, only ¼ grain of codeine phosphate is supplied to relieve the more severe pain that usually requires ½ grain. **Composition:** Same as Soma Compound plus ¼ grain codeine phosphate. **Dosage:** 1 or 2 tablets q.i.d. **Supplied:** Bottles of 50 white, lozenge-shaped tablets; subject to Federal Narcotics Regulations.

References available on request.

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ADOLPH'S is the salt substitute that solves the dieter's problem by saving the flavor! Looks, sprinkles and seasons like salt — and at the same time helps to provide supplemental potassium needed in low-sodium diets. At grocery stores everywhere. For free shaker samples write Adolph's Ltd., Burbank, California.

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Usual dose 2 Tbs. twice a day. Available, liquid and powder, 8 and 16 oz. bottles at pharmacies.

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(1) Brooks, L. H.: Dis. of Colon & Rectum, v. 1, no. 5, 1958

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then back
to the grind?
nutritional
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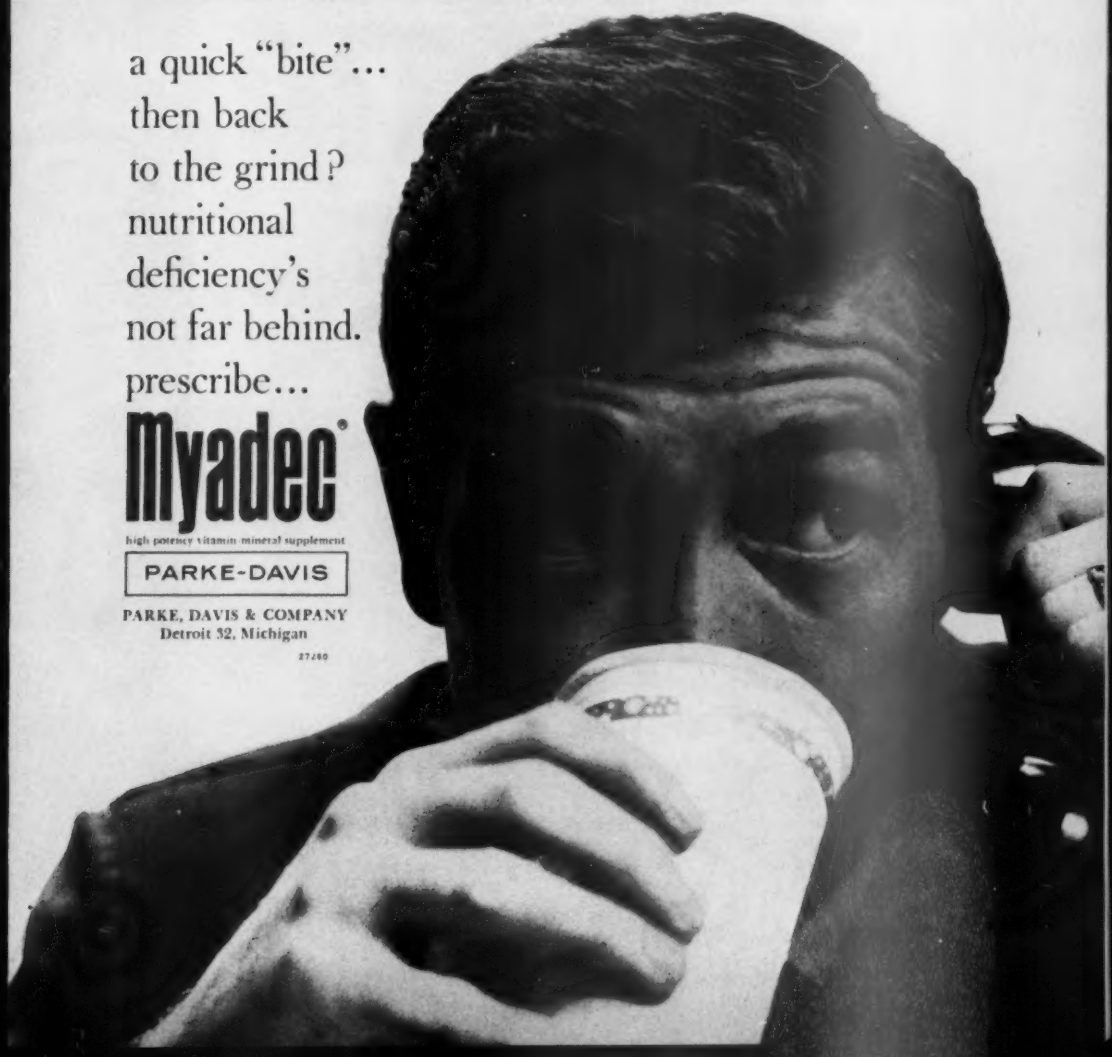

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ARAMINE®

METARAMINOL

provides combined pressor, myocardium-stimulating effect with no tissue slough reported

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ARAMINE can be administered for balanced pressor, myocardium-stimulating effect by any desired route—intravenous, intramuscular or subcutaneous—with no reported tissue slough and with minimal risk of causing arrythmias. Repeated injections of ARAMINE appear to elicit no tachyphylactic response.

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1. Selzer, A. and Rytand, D.A.: COUNCIL ON DRUGS, Report to Council J.A.M.A. 168:762, (Oct. 11) 1958.

MSD
MERCK SHARP & DOHME
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"comprehensive" multivitamins—friend or foe?

Although not itself harmful, the small amounts of folic acid in "comprehensive" multivitamins can correct significant blood disorders to confuse the diagnosis and delay the treatment of pernicious anemia victims.[1-13] Peripheral blood and bone marrow data may appear normal[1] in such patients while accompanying nerve degeneration continues. Diagnosis delayed by normal appearing indices can thus allow irreparable neurologic damage to occur before the true nature of the disease is recognized and treatment begun.[4]

To help physicians avoid this threat, Robins has formulated Adabee®, a new therapeutic multivitamin without folic acid, that is especially safe for long-term nutritional therapy in patients who require maximum support.

why no vitamin B_{12} in Adabee®?

In order to obtain therapeutic levels of specific vitamins for certain individual deficiencies, doctors must often employ a "comprehensive" multivitamin.[4,7] Many such elongated formulas include as ingredients substances which are nonessential, expensive to the patient, and irrational.[4,7,10]

On the basis that B_{12} in therapeutic vitamin mixtures has been described as needless by the A. M. A.,[2] and its unnecessary[9,10,14,15] and indiscriminate use[1] has been criticized by astute hematologists,[7] internists,[10] pathologists,[12,13] and nutritional workers,[2] this member of the B-complex has also been omitted from Adabee.

In a rational formula,[2,4,16,17] the need for hormones, enzymes, amino acids, or yeast is not supported. And since these superfluous substances might encumber the desired response to concurrently administered drugs, they are not found in the Adabee formulas.

Each yellow, capsule-shaped Adabee® tablet contains:

Vitamin A	25,000 USP units
Vitamin D	1,000 USP units
Thiamine mononitrate (B_1)	15 mg.
Riboflavin (B_2)	10 mg.
Pyridoxine HCl (B_6)	5 mg.
Nicotinamide (niacinamide)	50 mg.
Calcium pantothenate	10 mg.
Ascorbic acid (vitamin C)	250 mg.

Each green, capsule-shaped Adabee®-M tablet contains Adabee, plus nine minerals:

Iron	15.0 mg.
Iodine	0.15 mg.
Copper	1.0 mg.
Manganese	1.0 mg.
Magnesium	6.0 mg.
Zinc	1.5 mg.
Potassium	5.0 mg.
Calcium	103.0 mg.
Phosphorus	80.0 mg.

references:

1. Ellison, A. B. C., J.A.M.A., 173:240, 1960. 2. White, P. L., Sec'y, A.M.A. Council on Foods and Nutrition, J.A.M.A., 169:41, 1959. 3. New Eng. J. M., Vol. 259, No. 25, Dec. 18, 1958, p. 1231. 4. Goodman, L. S., and Gilman, A., *The Pharmacological Basis of Therapeutics*, 2nd ed., New York, Macmillan, 1955, pp. 1709-10, 1489-91. 5. *Federal Register*, Vol. 25, No. 136, July 14, 1960, p. 6633. 6. Conley, C. L., and Krevans, J. R., New Eng. J. M., 245:529-31, 1951. 7. Wintrobe, M. M., *Clinical Hematology*, 3rd ed., Phila., Lea & Febiger, 1952, pp. 398-400. 8. Frohlich, E. D., New Eng. J. M., 259:1221, 1958. 9. Vilter, R. W., *Modern Medicine*, 28:15, p. 90, Aug. 1960. 10. Bean, W. B., *Drugs of Choice: 1960-61*, W. Modell, ed., St. Louis, C. V. Mosby Co., 1960, pp. 115-16. 11. Crosby, W. H., Col., M.C., U.S.A., *Military Medicine*, 125:233, April, 1960. 12. Harris, C. E. C., Conn. State Med. J., pp. 543-45, July 1958. 13. Todd, Sanford, and Wells, *Clinical Diagnosis By Laboratory Methods*, 12th ed., W. B. Saunders, Phila., 1954, pp. 306-7. 14. Goldsmith, G. A., Am. J. of M., 25:660, Nov. 1958. 15. Darby, W. J., Am. J. of M., 25:726, Nov. 1958. 16. *GP*, Vol. XVIII, No. 2, p. 119, Aug. 1958. 17. J.A.M.A., Vol. 173, No. 16, pp. 1831-32, 1960.

the multivitamin without folic acid . . . or B_{12}

new! Adabee®

A. H. Robins Co., Inc.
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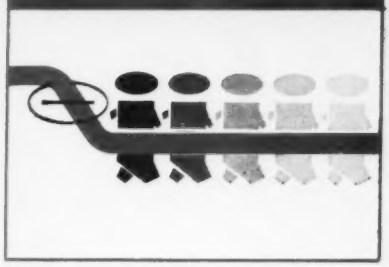
making oral blood-sugar control a reality for more diabetics

Diabinese®

brand of chlorpropamide



IN BRIEF

DIABINESE, a potent sulfonylurea, provides smooth, long-lasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, DIABINESE often works where other agents have failed to give satisfactory control.

INDICATIONS: **Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.**

ADMINISTRATION AND DOSAGE: **Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.**

Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used: most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: **In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, DIABINESE should be discontinued.**

PRECAUTIONS AND CONTRAINDICATIONS: **If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.**

SUPPLIED: **As 100 mg. and 250 mg. scored chlorpropamide tablets.**

More detailed professional information available on request.

Science for the world's well-being™

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Division, Chas. Pfizer & Co., Inc.
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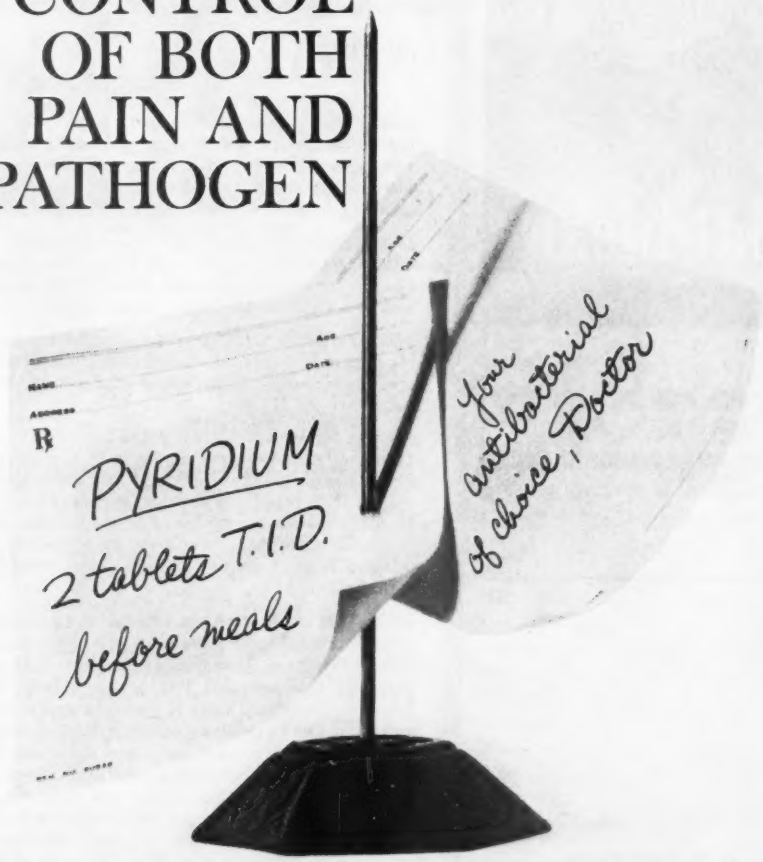
in painful urinary infections

PRECISE CONTROL OF BOTH PAIN AND PATHOGEN



For the patient: FREEDOM FROM PAIN
Pyridium relieves pain, burning, urgency and frequency in 30 minutes. Unlike fixed urinary analgesic/antibacterial combinations, Pyridium analgesia can be continued as needed...stopped...or resumed if pain occurs.

For the physician: FREEDOM OF CHOICE
Freed from the restrictions of fixed analgesic/antibacterial combinations, the physician can choose the urinary antibacterial most specific for the infection. In making *your* choice of antibacterial, consider Mandelamine.®

PYRIDIUM®
brand of phenylazo-diamino-pyridine HCl

WARNER CHILCOTT
MORRIS PLAINS, N.J.

stops urinary pain in 30 minutes

PY-6P03

for urinary infections

BACTERIAL CONTROL WITHOUT RESISTANT MUTANTS

As resistance develops to more and more antibacterials, many physicians choose Mandelamine as their antibacterial of first choice in urinary infections. Mandelamine acts *specifically* in the urinary tract, and is effective against most urinary pathogens (including antibiotic-resistant Staph.). Resistant strains have not developed. Sensitization in any form has not occurred, even after prolonged use...and Mandelamine is economical, too.

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MORRIS PLAINS, N.J.

MANDELAMINE®

brand of methenamine mandelate

the urine-specific antibacterial

MA-6P09

Three major criteria for an effective laxative have been established by physicians*

1. freedom from griping or other irritating side effects

2. clinically proven effectiveness

3. predictable action

*Results of a survey of over 1,000 physicians conducted by the Bureau of Research, Inc., 555 W. Jackson Blvd., Chicago 6, Illinois (April, 1960).

PERI-COLACE®

Anthraquinone derivatives from cascara and dioctyl sodium sulfosuccinate, Mead Johnson

meets physicians' criteria for an effective laxative

With Peri-Colace "...side effects such as griping are reduced to a minimum."[1]

Peri-Colace, a unique combination of Peristim® and Colace® (dioctyl sodium sulfosuccinate) "...gave satisfactory results in 97 per cent of the cases [130 hospitalized patients]."[2]

Experience in practice has shown the unusual dependability of Peri-Colace.[1-4] It promptly, yet gently, induces bowel evacuation within 8 to 12 hours in most patients.

References: (1) Broders, A. C., Jr.: Am. J. Digest. Dis. *2*:483-486 (Sept.) 1957. (2) Lamphier, T. A.: Am. J. Proctol. *8*:442-444 (Dec.) 1957. (3) Smigel, J. O.; Lowe, K. J.; Hosp, P. H., and Gibson, J. H.: M. Times *86*:1521-1526 (Dec.) 1958. (4) Turell, R.: Curr. M. Dig. *26*:61-69 (Feb.) 1959.

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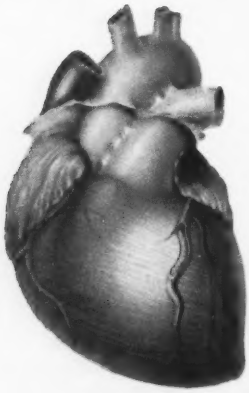
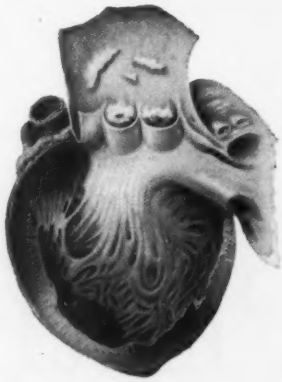


IN ANGINA PECTORIS AND CORONARY INSUFFICIENCY

... the treatment must go further than vasodilation alone. It should also control the patient's ever-present anxiety about his condition, since anxiety itself may bring on further attacks.



AFTER MYOCARDIAL INFARCTION

... it is frequently not enough to boost blood flow through arterial offshoots and establish new circulation. The disabling fear and anxiety that invariably accompany the condition must be reduced, or the patient may become a chronic invalid.

Protects your angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, considerably delay recovery.

This is why Miltrate gives better protection for the heart than vasodilation alone in coronary insufficiency, angina pectoris and postmyocardial infarction. Miltrate contains not only PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. What is more important – Miltrate provides Miltown, a tranquilizer of *proven* effectiveness in relieving anxieties, fear and day-to-day tension in over 600 clinical studies.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition...and his operative arteries are dilated to enhance myocardial blood supply.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.
Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

REFERENCES

1. Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J. E. F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

Miltrate®

Miltown® (meprobamate) + PETN

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CML-1360

UNSURPASSED "GENERAL-PURPOSE" CORTICOSTEROID...

Aristocort®

Triamcinolone LEDERLE

OUTSTANDING FOR "SPECIAL-PURPOSE" THERAPY

Lederle

Aristocort

Triamcinolone has long since proved its unsurpassed efficacy and relative safety in the therapy of *rheumatoid arthritis, inflammatory and allergic dermatoses, bronchial asthma,* and all other conditions in which corticosteroids are indicated. But ARISTOCORT has also opened up new areas of therapy for selected patients who otherwise could not be given corticosteroids. Medicine is now in an era of "special-purpose" steroids.[1]

One outstanding advantage of triamcinolone is that it rarely produces edema and sodium retention.[1, 2]

The clinical importance of this property cannot be overemphasized in treating certain types of patients. McGavack and associates[3] have reported the beneficial results with ARISTOCORT in patients with existing or impending cardiac failure, and those with obesity associated with lymphedema. Triamcinolone, in contrast to most other steroids, is not contraindicated in the presence of edema or impending cardiac decompensation.[3]

Hollander[1] points out the superiority of triamcinolone in not causing mental stimulation, increased appetite and weight gain, compared to other steroids which produce these effects in varying degrees. And McGavack,[2] in a comparative tabulation of steroid side effects, indicates that triamcinolone does not produce the increased appetite, insomnia, and psychic disturbances associated with other newer steroids.

ARISTOCORT can thus be advantageous for patients requiring corticosteroids whose appetites should not be stimulated, and for those who are already overweight or should not gain weight. Likewise, ARISTOCORT is suitable for the many patients with emotional and nervous disorders who should not be subjected to psychic stimulation. Furthermore, ARISTOCORT Triamcinolone, in effective doses, showed a low incidence of side reactions and is a steroid of choice for treating the older patient in whom salt and water retention may cause serious damage.[2]

References: 1. Hollander, J. L.: *J.A.M.A.* 172:306 (Jan. 23) 1960. 2. McGavack, T. H.: *Nebraska M. J.* 44:377 (Aug.) 1959. 3. McGavack, T. H.; Kao, K. Y. T.; Leake, D. A.; Bauer, H. G., and Berger, H. E.; *Am. J. M. Sc.* 236:720 (Dec.) 1958.

Precautions: Collateral hormonal effects generally associated with corticosteroids may be induced. These include Cushingoid manifestations and muscle weakness. However, sodium and potassium retention, edema, weight gain, psychic aberration and hypertension are exceedingly rare. Dosage should be individualized and kept at the lowest level needed to control symptoms. It should not exceed 36 mg. daily without potassium supplementation. Drug should not be withdrawn abruptly. Contraindicated in herpes simplex and chicken pox.

Supplied: Scored tablets — 1 mg. (yellow); 2 mg. (pink); 4 mg. (white); 16 mg. (white).

Lederle

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

to favor recovery in FIBROSIS...

Prescribe adequate daily amounts of

POTABA*

(Pure Potassium Aminobenzoate, Glenwood)

Institute treatment early and continue for a long enough period.

Evidence obtained from the observations of competent clinical investigators justifies the suggestion that this non-toxic drug may be found of great value wherever the pathological formation of fibrous tissue retards the patient's response to treatment.

Marked improvement in Scleroderma following treatment with POTABA prompted its use in *treatment resistant* Sarcoidosis and Peyronie's disease with the following recently reported results:

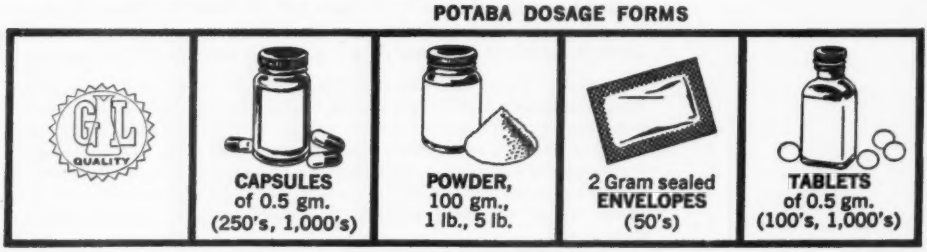
In 15 cases of Sarcoidosis cough, dyspnea and malaise decreased in 14. Partial or complete clearing of x-ray abnormalities was evident in 13 patients.[1]

21 Patients with Peyronie's disease receiving 12 gms. daily in divided doses for periods ranging from 3 months to 2 years responded as follows: Pain, where present disappeared from 16 of 16 cases. Penile deformity improved in 14 of 17 patients. Plaque decreased in 16 of 21.[2]

1. Cohen, R. V., Lambert, R. L., and Molthan, L.: The Use of POTABA in Sarcoidosis; Annual Meeting American Trudeau Society, Eastern Section, Boston, Mass. (1958).

2. Zarafonetis, C. J. D., and Horrax, T. M.: Treatment of Peyronie's Disease with POTABA, Journal of Urology, 81: 770-772 (June 1959).

POTABA DOSAGE FORMS



Please request information on POTABA and PASKALIUM

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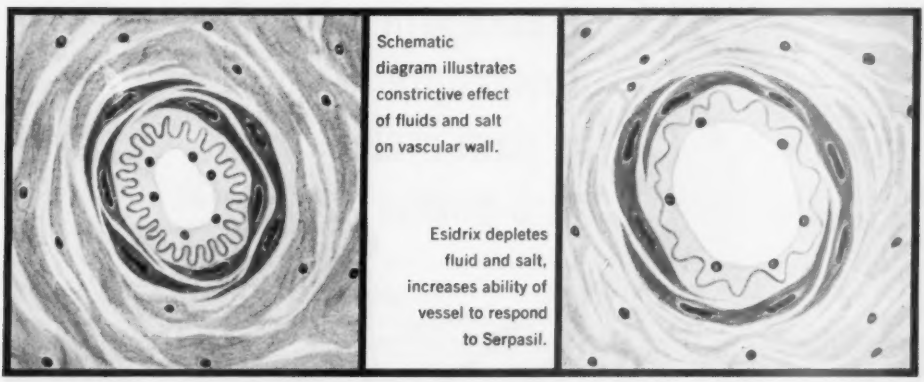
GLENWOOD LABORATORIES INC. / BERGENFIELD, N. J.

Why combining Esidrix® with Serpasil® improves control of high blood pressure

The presence of excess tissue fluids and salt can keep constricted blood vessels from dilating fully in response to antihypertensive drugs. ■ This may explain why the antihypertensive effect of Serpasil-Esidrix is better than average. By depleting fluid and electrolytes from surrounding tissue, Esidrix enables blood vessels to dilate to physiologic limits. Result: Peripheral resistance is reduced and blood pressure goes down—often to lower levels than can be achieved with single-drug therapy. Complete information sent on request.


Schematic diagram illustrates constrictive effect of fluids and salt on vascular wall.
Esidrix depletes fluid and salt, increases ability of vessel to respond to Serpasil.

SUPPLIED: **Tablets #2** (light orange), each containing 0.1 mg. Serpasil and 50 mg. Esidrix. **Tablets #1** (light orange) each containing 0.1 mg. Serpasil and 25 mg. Esidrix. SERPASIL®-ESIDRIX® (reserpine and hydrochlorothiazide CIBA)

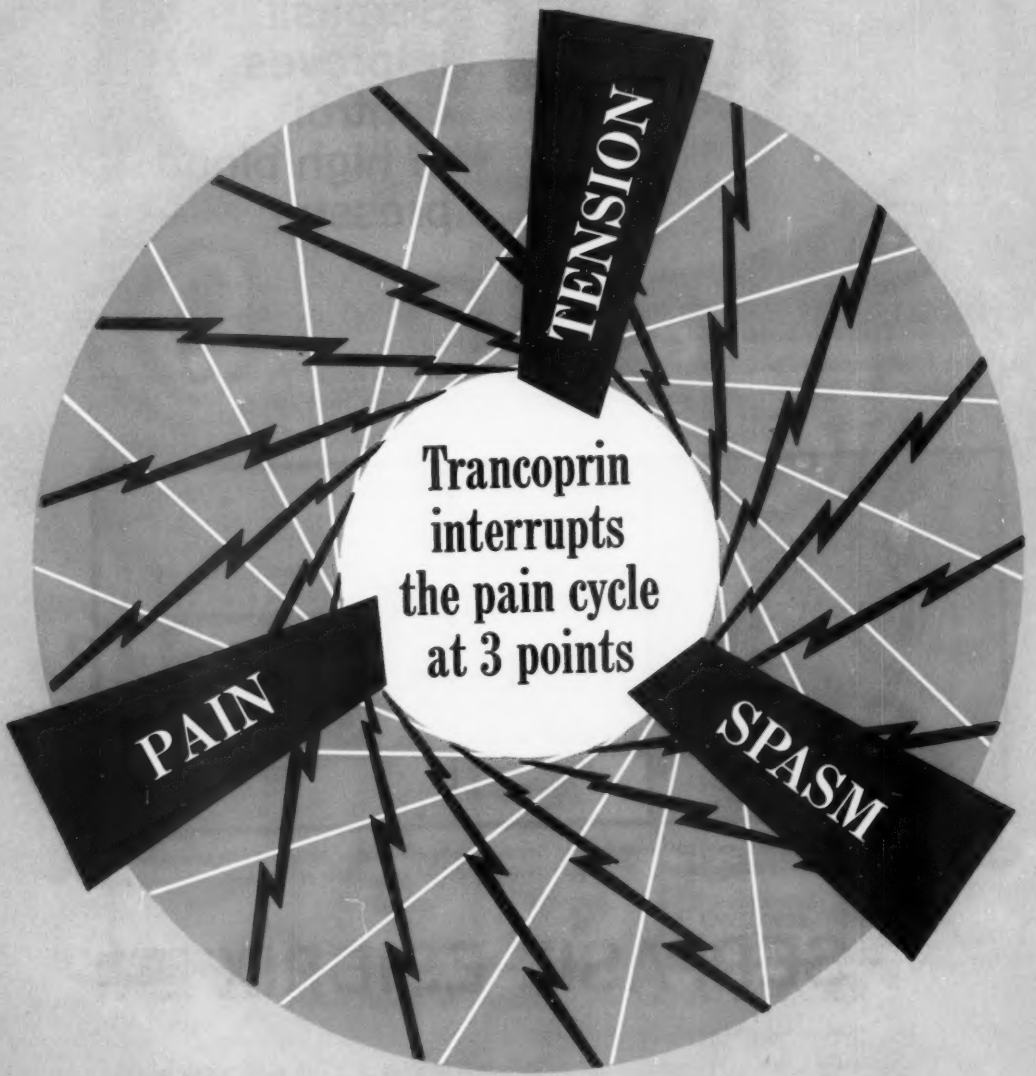
SERPASIL®-ESIDRIX® CIBA SUMMIT, N. J.

announcing...

Trancoprin®

acetylsalicylic acid (300 mg.) and chlormezanone (50 mg.)

Tablets



a broad spectrum non-narcotic analgesic

Trancoprin, a new analgesic, not only raises the pain perception threshold but, through its chlormezanone component, also relaxes skeletal muscle spasm[1-6] and quiets the psyche.[2,3-5,7]

The effectiveness of Trancoprin has been demonstrated clinically[8] in a number of patients with a wide variety of painful disorders ranging from headache, dysmenorrhea and lumbago to arthritis and sciatica. In a series of 862 patients,[8] Trancoprin brought excellent or good relief of pain to 88 per cent of the group. In another series,[9] Trancoprin was administered in an industrial dispensary to 61 patients with headache, bursitis, neuritis or arthritis. The excellent results obtained prompted the prediction that Trancoprin "... will prove a valuable and safe drug for the industrial physician."[9]

Exceptionally Safe

No serious side effects have been encountered with Trancoprin. Of 923 patients treated with Trancoprin, only 22 (2.4 per cent) experienced any side effects.[8,9] In every instance, these reactions, which included temporary gastric distress, weakness or sedation, were mild and easily reversed.

Indications

Trancoprin is recommended for more comprehensive control of the pain complex (pain → tension → spasm) in those disorders in which tension and spasm are complicating factors, such as: headaches, including tension headaches / premenstrual tension and dysmenorrhea / low back pain, sciatica, lumbago / musculoskeletal pain associated with strains or sprains, myositis, fibrositis, bursitis, trauma, disc syndrome and myalgia / arthritis (rheumatoid or hypertrophic) / torticollis / neuralgia.

Dosage

The usual adult dosage is 2 Trancoprin tablets three or four times daily. The dosage for children from 5 to 12 years of age is 1 tablet three or four times daily. Trancoprin is so well tolerated that it may be taken on an empty stomach for quickest effect. The relief of symptoms is apparent in from fifteen to thirty minutes after administration and may last up to six hours or longer.

How Supplied

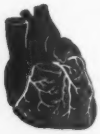
Each Trancoprin tablet contains 300 mg. (5 grains) of acetylsalicylic acid and 50 mg. of chlormezanone [Trancopal® brand]. Bottles of 100 and 1000.

Trancoprin Tablets / **non-narcotic analgesic**

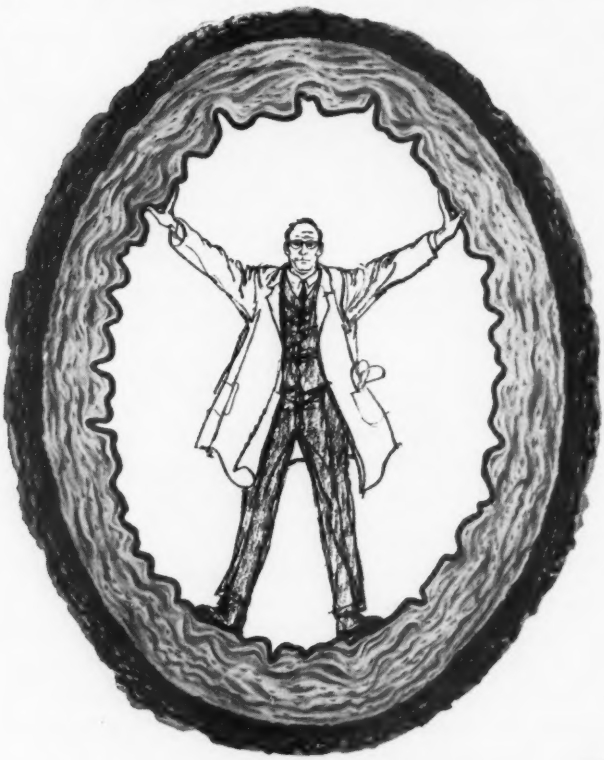
References: 1. DeNyse, D. L.: *M. Times* 87:1512, Nov., 1959. 2. Ganz, S. E.: *J. Indiana M. A.* 52:1134, July, 1959. 3. Gruenberg, Friedrich: *Current Therap. Res.* 2:1, Jan., 1960. 4. Kearney, R. D.: *Current Therap. Res.* 2:127, April, 1960. 5. Lichtman, A. L.: *Kentucky Acad. Gen. Pract. J.* 4:28, Oct., 1958. 6. Mullin, W. G., and Epifano, Leonard: *Am. Pract. & Digest Treat.* 10:1743, Oct., 1959. 7. Shanaphy, J. F.: *Current Therap. Res.* 1:59, Oct., 1959. 8. Collective Study, Department of Medical Research, Winthrop Laboratories. 9. Hergesheimer, L. H.: An evaluation of a muscle relaxant (Trancopal) alone and with aspirin (Trancoprin) in an industrial medical practice, to be submitted.

Winthrop LABORATORIES, New York 18, N. Y.

Trancoprin and Trancopal (brand of chlormezanone) trademarks reg. U.S. Pat. Off.



in coronary insufficiency



Metamine® Sustained* helps you dilate the coronaries

METAMINE SUSTAINED (triethanolamine trinitrate biphosphate, 10 mg., in a unique sustained-release tablet) is a potent and exceptionally well tolerated coronary vasodilator. Pharmacological studies at McGill University demonstrated that METAMINE "exerts a more prolonged and as good, if not slightly better coronary vasodilator action than nitroglycerin . . ."[1] Work at the Pasteur Institute established that METAMINE exerts considerably less depressor effect than does nitroglycerin.[2] Virtually free from nitrate side effects (nausea, headache, hypotension), METAMINE SUSTAINED protects many patients refractory to other cardiac nitrates,[3] and, given b.i.d., is ideal medication for the patient with coronary insufficiency. Bottles of 50 and 500 tablets. Also: METAMINE, METAMINE WITH BUTABARBITAL, METAMINE WITH BUTABARBITAL SUSTAINED, METAMINE SUSTAINED WITH RESERPINE.

1. Melville, K. I., and Lu, F.C.: Canadian M.A.J., *65*:11, 1951. 2. Bovet, D., and Nitti-Bovet, F.: Arch. Internat. de pharmacodyn. et therap., *83*:367, 1946. 3. Fuller, H. L., and Kassel, L.E.: Antibiotic Med. & Clin. Therapy, *3*:322, 1956.

Thos. Leeming & Co. Inc. New York 17, N. Y. *Patent applied for

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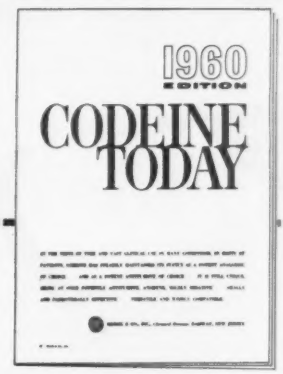
NEW FACTS ABOUT CONTROLLING PAIN AND COUGH

New Comprehensive Supplement to 'Codeine Today' Highlights Newest Data on One of Medicine's Most Useful but Underestimated Drugs



Just 20 minutes reading will review for you essential clinical findings on the use of Codeine. New supplement presents concise quotes by today's authorities on the use of codeine in conditions from the common cold to sickle cell disease. Tells when to use, how to use and where to use this versatile drug. Supplement is attached to 'Codeine Today' which reviews 1957-1958 data. This information is of interest to practically every practitioner. Bibliography now totals more than 80 references.

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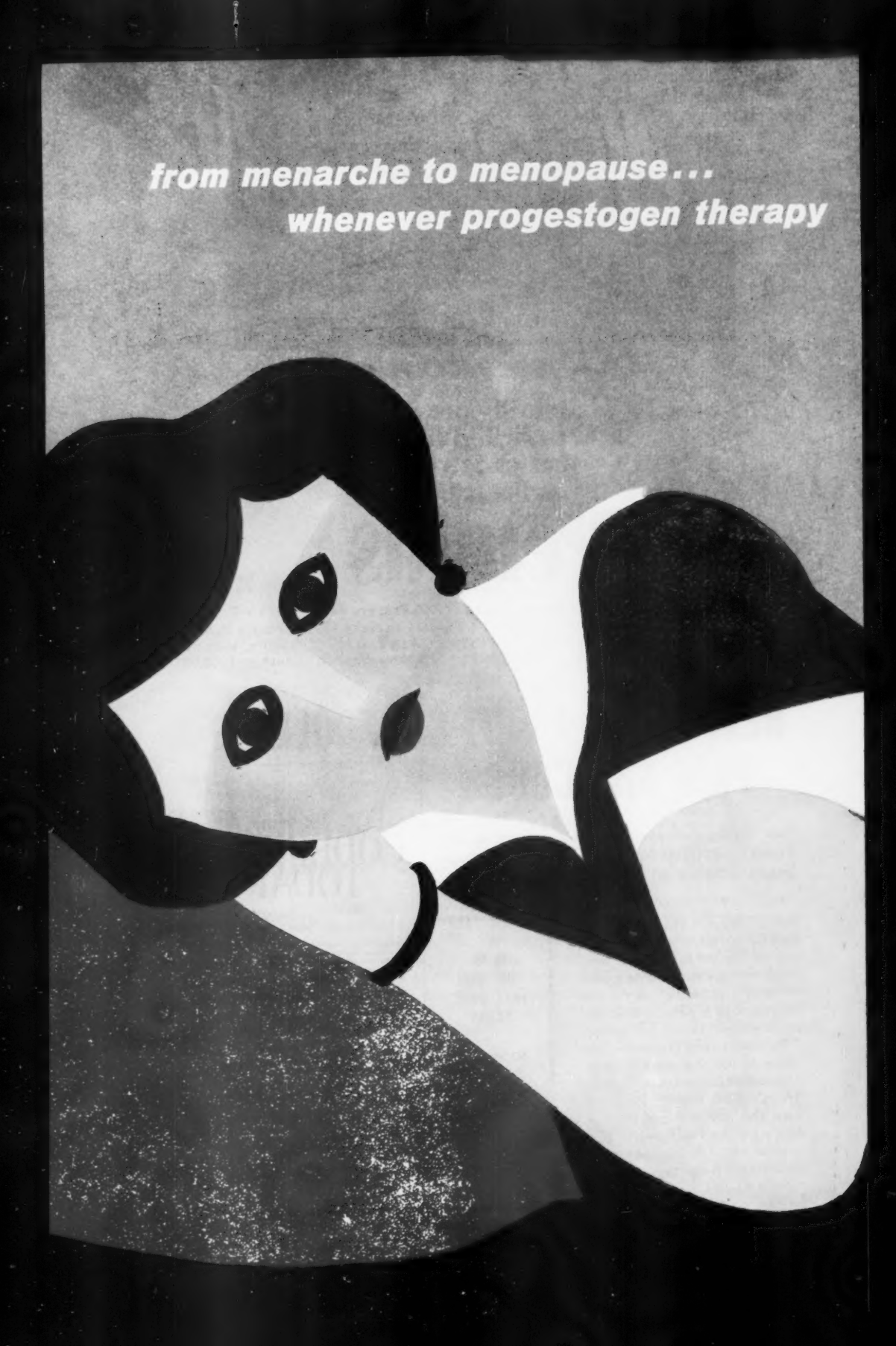
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Is advisable

NORLUTIN®

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oral progestational agent

NORLUTIN has been found "...remarkably efficacious in relief of many disturbances of menstruation and reproduction."* Such disorders of hormonal origin respond to therapy physiologically because NORLUTIN has a marked capacity for normalizing the estrogen-progestogen ratio. And since this agent eliminates the need for injections, it wins wider patient acceptance.

Indications: amenorrhea • functional uterine bleeding • endocrine infertility • habitual abortion • threatened abortion • dysmenorrhea • premenstrual tension

Supplied: 5-mg. scored tablets, bottles of 30.

*Rock, J.; Garcia, C. R., & Pincus, G.: *Am. J. Obst. & Gynec.* 79:758, 1960.

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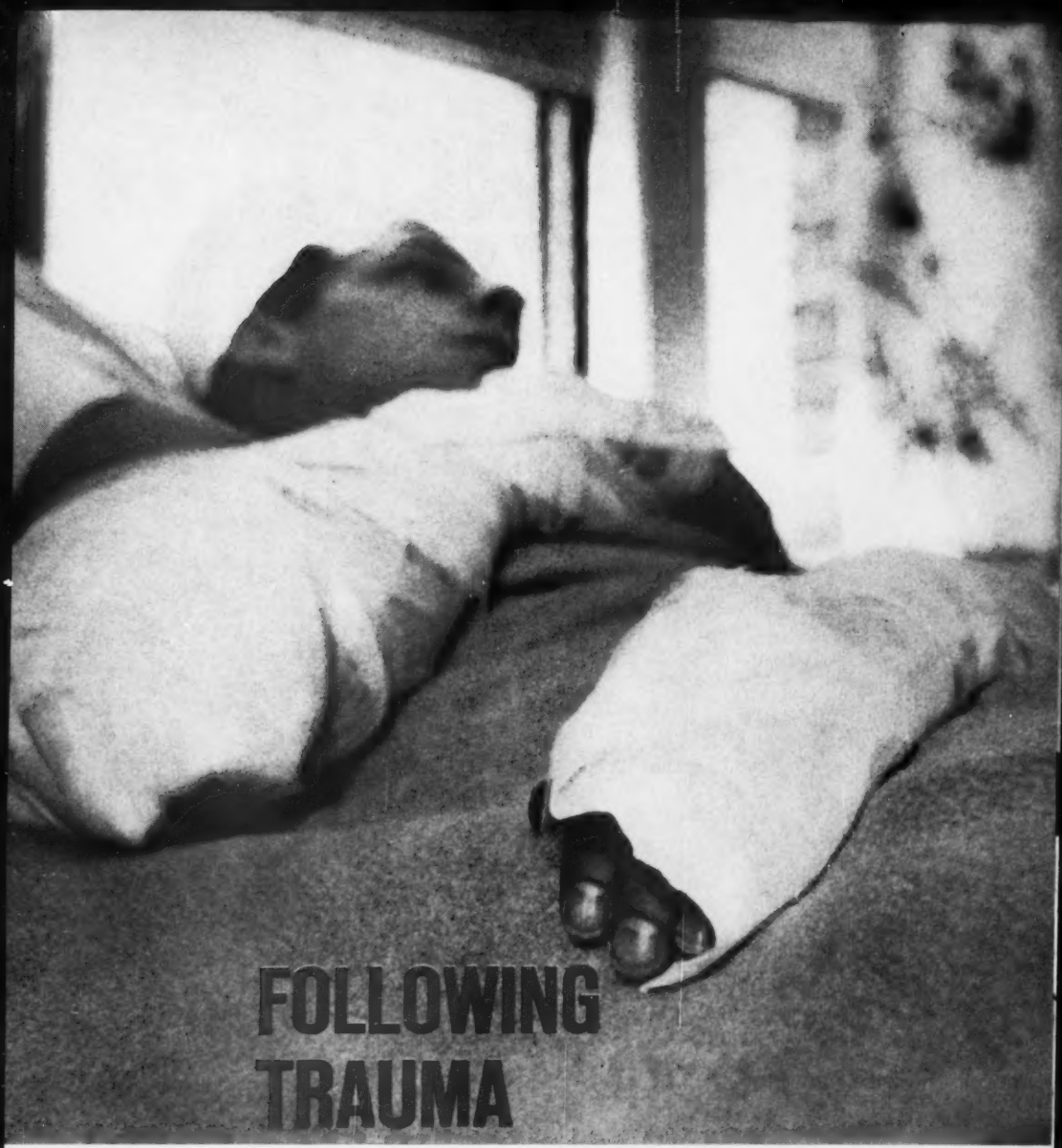

nutritional therapy in the "therapeutic" jar

STRESSCAPS helps meet increased metabolic requirements in burns, fractures and wounds. Abnormal levels of water-soluble vitamins are suddenly required with other nutritional factors—just as the stress reaction induces severe depletion[1,2] and alters metabolism.[3] High potency supplements must be administered[1,2] as provided by STRESSCAPS, to support rapid recovery and prevent general complications of metabolic failure. Of "therapeutic" importance to the out-patient, the attractive STRESSCAPS jar is a convenient reminder of daily dosage... insuring adequate intake over the therapeutic course.

Each capsule contains: Thiamine Mononitrate (B_1) 10 mg., Riboflavin (B_2) 10 mg., Niacinamide 100 mg., Ascorbic Acid (C) 300 mg., Pyridoxine HCl (B_6) 2 mg., Vitamin B_{12} 4 mcgm., Calcium Pantothenate 20 mg., Vitamin K (Menadione) 2 mg. Average dose: 1-2 capsules daily.

1. Richardson, M. E.: J. Am. Osteop. A. 57:562 (May) 1958. 2. Mason, M. L.: Northwest Med. 57:1439 (Nov.) 1958. 3. Coleman, S. S.: Am. J. Surg. 97:43 (Jan.) 1959.

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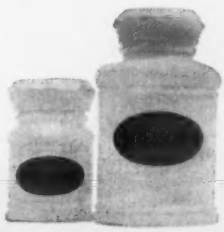
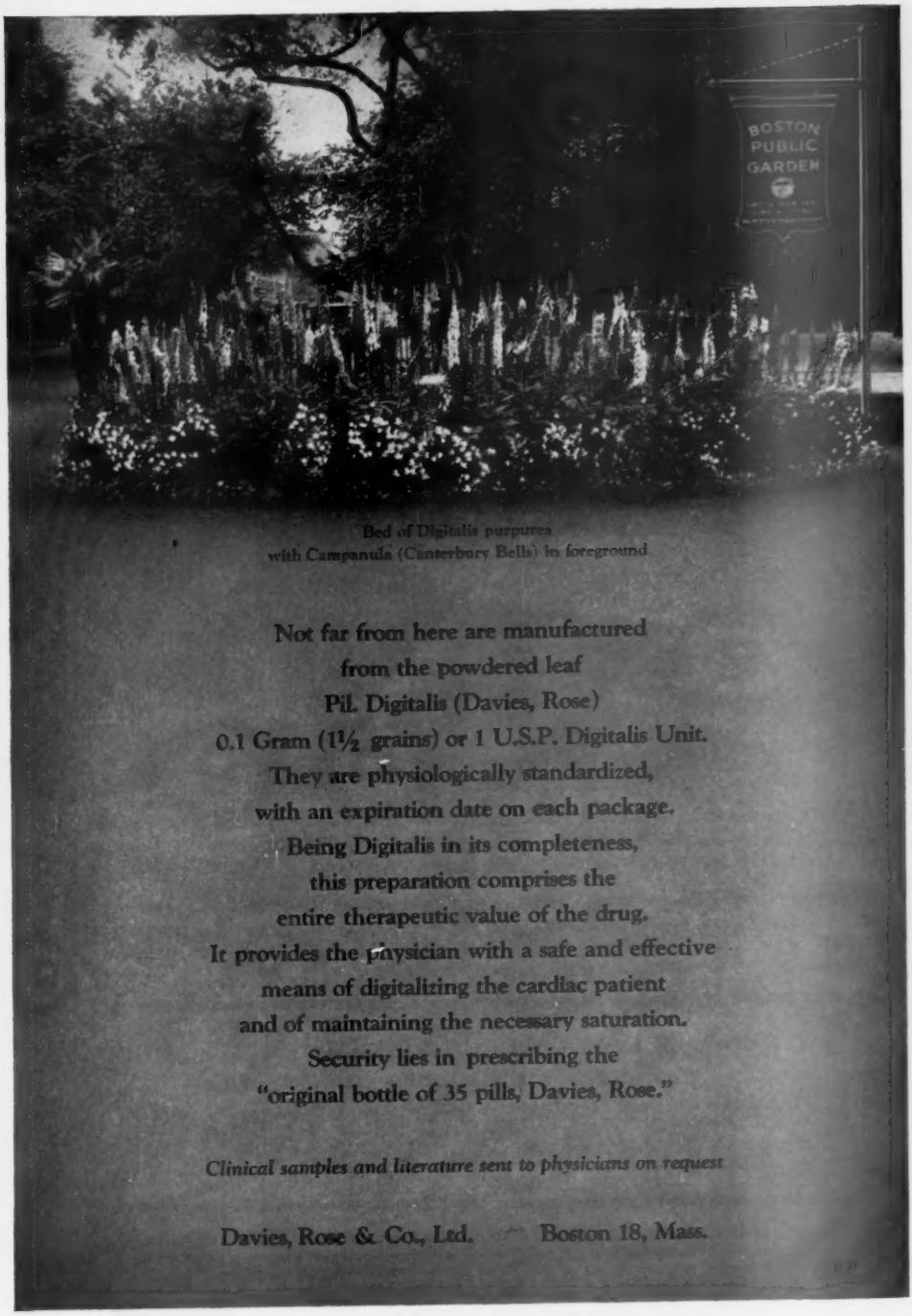
STRESSCAPS®

Stress Formula Vitamins Lederle





Bed of Digitalis purpurea
with Campanula (Canterbury Bells) in foreground

Not far from here are manufactured
from the powdered leaf
Pil. Digitalis (Davies, Rose)
0.1 Gram (1½ grains) or 1 U.S.P. Digitalis Unit.
They are physiologically standardized,
with an expiration date on each package.
Being Digitalis in its completeness,
this preparation comprises the
entire therapeutic value of the drug.
It provides the physician with a safe and effective
means of digitalizing the cardiac patient
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Security lies in prescribing the
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this hypertensive patient prefers Singoserp . . . and so does his physician

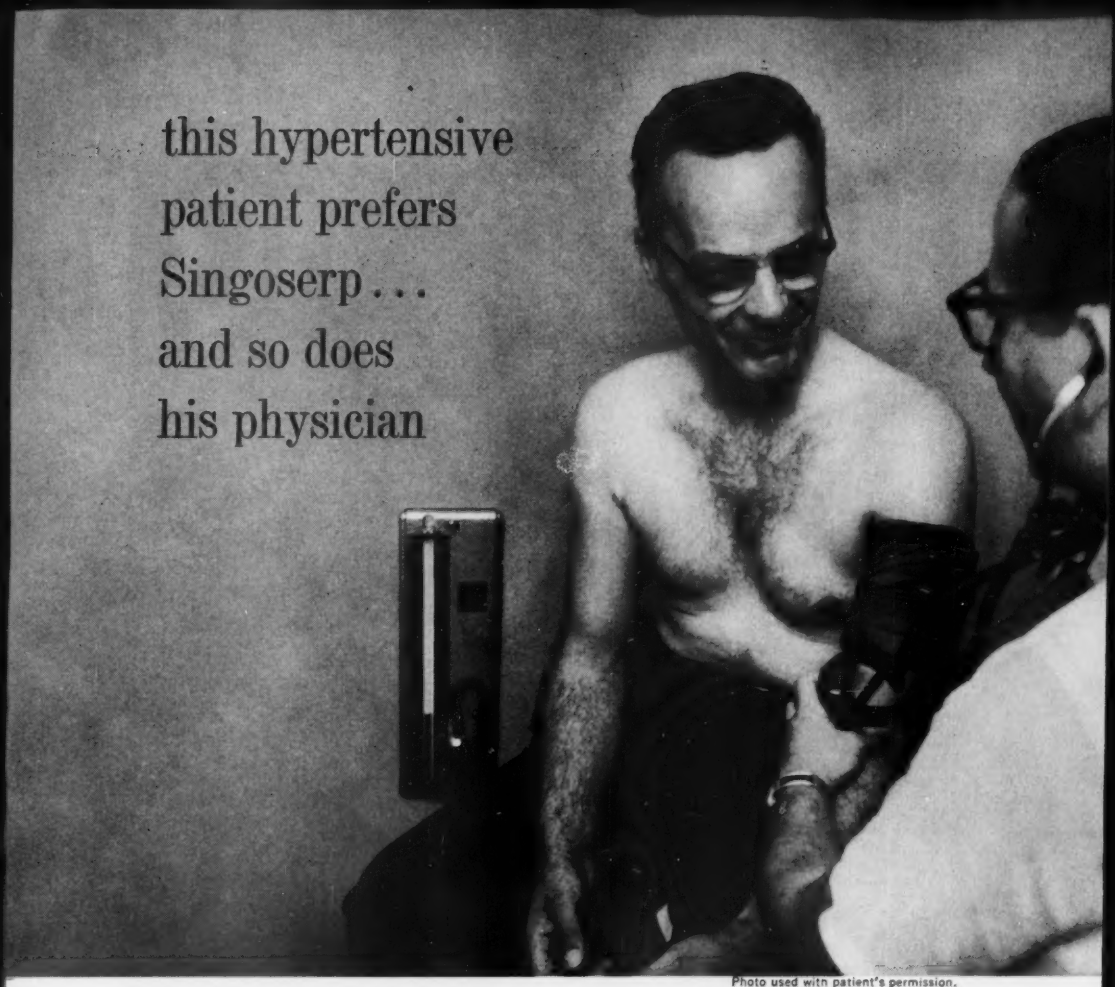

Photo used with patient's permission.

Patient's comment: "The other drug [whole root rauwolfia] made me feel lazy. I just didn't feel in the mood to make my calls. My nose used to get stuffed up, too. This new pill [Singoserp] doesn't give me any trouble at all."

Clinician's report: J. M., a salesman, had a 16-year history of hypertension. Blood pressure at first examination was 190/100 mm. Hg. Whole root rauwolfia lowered pressure to 140/80 — but side effects were intolerable. Singoserp 0.5 mg. daily, further reduced pressure to 130/80 and eliminated all drug symptoms.

Many hypertensive patients and their physicians prefer Singoserp® because it usually lowers blood pressure without rauwolfia side effects

SUPPLIED: Singoserp **Tablets,** 1 mg. (white, scored). Also available: Singoserp®-Esidrix® **Tablets** #2 (white), each containing 1 mg. Singoserp and 25 mg. Esidrix; Singoserp®-Esidrix® **Tablets** #1 (white), each containing 0.5 mg. Singoserp and 25 mg. Esidrix. **Complete information sent on request.**

Singoserp® (syrosingopine CIBA)
Singoserp®-Esidrix® (syrosingopine and hydrochlorothiazide CIBA)

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she calls it "nervous indigestion"

diagnosis: a wrought-up patient with a functional gastrointestinal disorder compounded by inadequate digestion. **treatment:** reassurance first, then medication to relieve the gastric symptoms, calm the emotions, and enhance the digestive process. **prescription:** new Donnazyme—providing the multiple actions of widely accepted Donnatal® and Entozyme®—two tablets t.i.d., or as necessary.

Each Donnazyme tablet contains

—In the gastric-soluble outer layer: Hyoscyamine sulfate, 0.0518 mg.; Atropine sulfate, 0.0097 mg.; Hyoscine hydrobromide, 0.0033 mg.; Phenobarbital (1/8 gr.), 8.1 mg.; and Pepsin, N. F., 150 mg. **In the enteric-coated core:** Pancreatin, N. F., 300 mg., and Bile salts, 150 mg.

antispasmodic • sedative • digestant

DONNAZYME®

A. H. ROBINS COMPANY, INCORPORATED • RICHMOND 20, VIRGINIA

relaxes muscle tension
raises pain threshold

"...continuous satisfactory control of the patient's painful state..."[1]

phenyramidol HCl

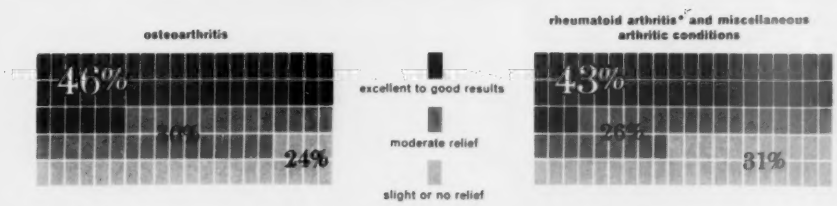
analexin®

relieves the total pain experience

Analexin is the only known drug to possess both analgesic and muscle relaxant properties in a single molecular structure.[2-4] These two distinct actions occurring simultaneously make Analexin a new class of drug...the first analgomylaxant. Where pain makes tension and tension makes pain, Analexin can more effectively relieve the total pain experience.

Analexin's range of analgesia is comparable to codeine, yet it is non-narcotic, not narcotic-related or habituating, and there is no evidence suggestive of tolerance or cumulative effects.[1-8] The incidence of side effects is low and their nature is usually mild and transient.[1,6-8]

"The resultant analgesia occurred promptly and persisted for at least 3 or 4 hours."[6]



*Patients who failed to respond included severe active rheumatoid arthritis not responding to any dosage scheme.

Analexin—for relief of pain. Each tablet contains 200 mg. phenyramidol HCl.

Analexin-AF—for relief of pain complicated by inflammatory processes. Each tablet contains 100 mg. phenyramidol HCl and 300 mg. aluminum aspirin.

References: 1. Batterman, R. C., *et al.*: Am. J. Med. Sc. *238*:315, 1959. 2. O'Dell, T. B.: Ann. New York Acad. Sc. *86*:191, 1960. 3. O'Dell, T. B., *et al.*: J. Pharmacol. & Exper. Therap. *128*:65, 1960. 4. O'Dell, T. B., *et al.*: Fed. Proc. *18*:1694, 1959. 5. Gray, A. P., *et al.*: J. Am. Chem. Soc. *81*:4347, 1959. 6. Wainer, A. S.: Ann. New York Acad. Sc. *86*:250, 1960. 7. Clinical data from the files of the Medical Department, Irwin, Neisler & Co., 1959, 1960. 8. Batterman, R. C.: Ann. New York Acad. Sc. *86*:203, 1960.

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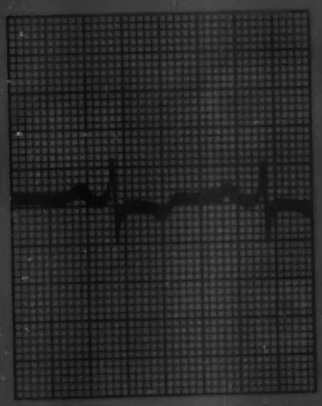
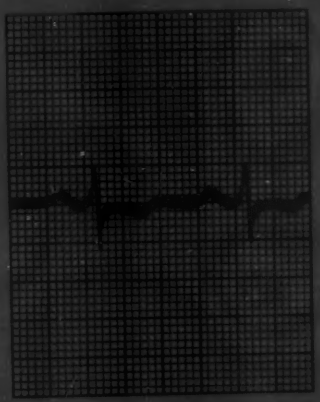
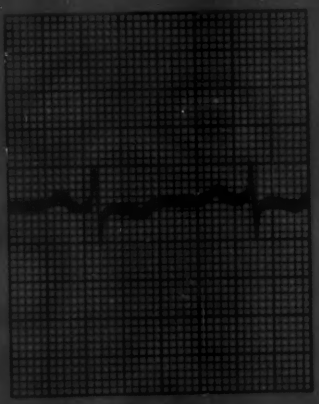


Lead II: at rest.



Lead II: 1½ minutes after 10 mg. TENUATE I.V.—equivalent to 100 mg. oral dose (4 times the recommended oral dose).



5 minutes after injection.

with Tenuate, ECG fluctuation is insignificant[1]

TENUATE

(diethylpropion)

hunger control with less than 1% CNS stimulation[2-8]

TENUATE suppresses appetite with unique advantages for "special risk" patients: no effect on heart rate, blood pressure, pulse or respiration,[1] no alteration of BMR.[2]

Dosage: One 25 mg. Tablet one hour before meals, or 1 new TENUATE DOSPAN Tablet (75 mg.) daily, in midmorning, swallowed whole. An additional 25 mg. Tablet may be taken in midevening to control nighttime hunger.

Supply: TENUATE Tablets (25 mg. each), bottles of 100 and 1000; TENUATE DOSPAN Tablets (75 mg. each), bottles of 100.

References: 1. Alfaro, R. D.; Graeanin, V. and Schlenker, E.: J. Lancet *(in press)*. 2. Houk, G.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 3. Herwick, S.: Personal communication, 1959. 4. Spielman, A. R.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 5. Ravets, E.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 6. Decina, L. J.: Exper. Med. & Surg. *(in press)*. 7. Seanian, J. S.: Personal communication, 1959. 8. Kroets and Starek: Personal communication, 1959.

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10 TO 12 HOUR HUNGER CONTROL WITH 1 TABLET

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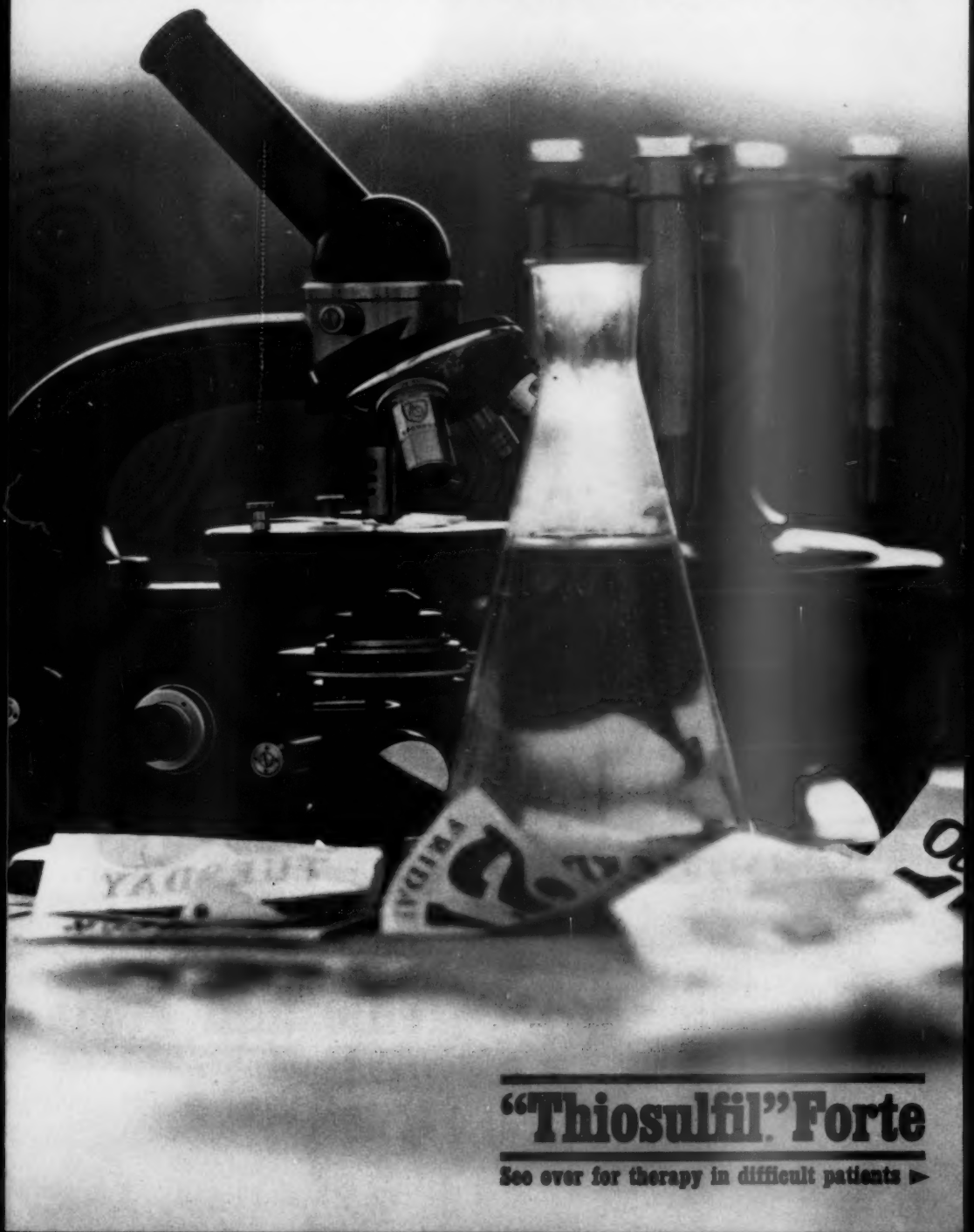
TRADEMARKS: TENUATE®, DOSPAN® (MERRELL'S CONTINUOUS RELEASE DOSAGE FORM)

THE SULFA COMPOUND THAT IS ESPECIALLY VALUABLE IN URINARY TRACT INFECTIONS BECAUSE IT CAN BE GIVEN SAFELY-WITHOUT INTERRUPTION—FOR WEEKS, MONTHS...EVEN YEARS.



"Thiosulfil" Forte

See over for therapy in difficult patients ►

HOW TO IMPROVE THE PROGNOSIS IN THE DIFFICULT PATIENT WITH URINARY TRACT INFECTION: Proof of effectiveness and record of safety in long term therapy are two important factors in the selection of a sulfa, particularly when the infection is stubborn and recurrent; occurs during pregnancy; in prostatitis; in patients with indwelling catheters; when stasis is a potential cause of ascending infection. "Thiosulfil" Forte is specially valuable in the treatment of problem patients with urinary tract infection as demonstrated by years of clinical experience.

RECORD OF SAFETY

In clinical studies of over 3,600 patients, the number of reactions, none serious, was less than 2 per cent.[1-6] " 'Thiosulfil' was remarkably well tolerated, there being no discontinuation of treatment due to untoward effects, and very few mild reactions were noted."[2] "The drug can be taken over a long period of time with practically no untoward side reactions."[3] "Clinical trial appears to indicate that the drug can be tolerated where other sulfa drugs cannot and that it is effective where some others are not."[4] Out of 3,057 cases . . . 47 patients (1.6%) showed g.i. disturbances and 33 patients (1.1%) allergic reactions.[1] NO REPORTS OF: hemorrhagic dyscrasias, hematuria, anuria, agranulocytosis.

PROOF OF EFFECTIVENESS

A review of more than 3,600 reported cases on "Thiosulfil" demonstrates: a) adequate drug dosage can be simply and economically achieved with a minimum incidence of complicating side effects; b) the antibacterial agent can be given over longer periods of time, particularly in cases involving urinary stasis.

Specific For Urinary Tract Infections: "Thiosulfil" reaches greater urinary concentrations in the active, free, nonmetabolized form than any other sulfa, single or mixed. "Thiosulfil" is rapidly excreted; as much as 79% of the drug is found in the urine after eight hours—of this, 98% is in the active form.[5] The entire g.u. tract is, thus, subjected to continual "sulfa baths" of active drug—more wide spectrum antibacterial activity at site of infection.

Even where urinary stasis exists and cannot be readily corrected, prolonged or even indefinite use of "Thiosulfil" on a reduced dosage schedule will usually keep the infection under control, patients comfortable, and side effects minimal. "Thiosulfil" may materially reduce the likelihood of infections ascending to the parenchyma of the kidneys and subsequent serious systemic involvement.

DOSAGE (Urinary Tract Infections)

TIME PERIOD	DOSE
First two weeks	3 Gm./day[1]
2 weeks to 3 months	2 Gm./day[2, 6]
3 months or longer	0.5 Gm./day[7]

Suggested Range of Dosage: 1 or 2 tablets three or four times daily. Note: The usual precautions exercised with sulfonamides should be observed.

Supplied: No. 786: Each tablet contains 0.5 Gm. sulfamethizole; in bottles of 100 and 1,000 scored tablets.

References—1. Bourque, J-P., and Gauthier, G-E.: Seven years' experience with sulfamethizole, to be published. 2. Bourque, J-P., and Joyal, J.: Canad. M.A.J. 68:337 (Apr.) 1953. 3. Barnes, R. W.: J. Urol. 71:655 (May) 1954. 4. Goodhope, C. D.: J. Urol. 72:552 (Sept.) 1954. 5. Boger, W. P.: The Antibacterial Sulfonamides: Comparative Studies, Scientific Exhibit Section, American Academy of General Practice Eleventh Annual Scientific Assembly, Apr. 6-9, 1959, San Francisco, California. 6. Cottrell, T. L. C., Rolnick, D., and Lloyd, F. A.: Rocky Mountain M. J. 56:66 (Mar.) 1959. 7. Hughes, J., Coppridge, W. M., and Roberts, L. C.: North Carolina M. J. 17:320 (July) 1956.

THE SULFA COMPOUND THAT IS ESPECIALLY VALUABLE IN URINARY TRACT INFECTIONS BECAUSE IT CAN BE GIVEN SAFELY—WITHOUT INTERRUPTION—FOR WEEKS, MONTHS...EVEN YEARS.

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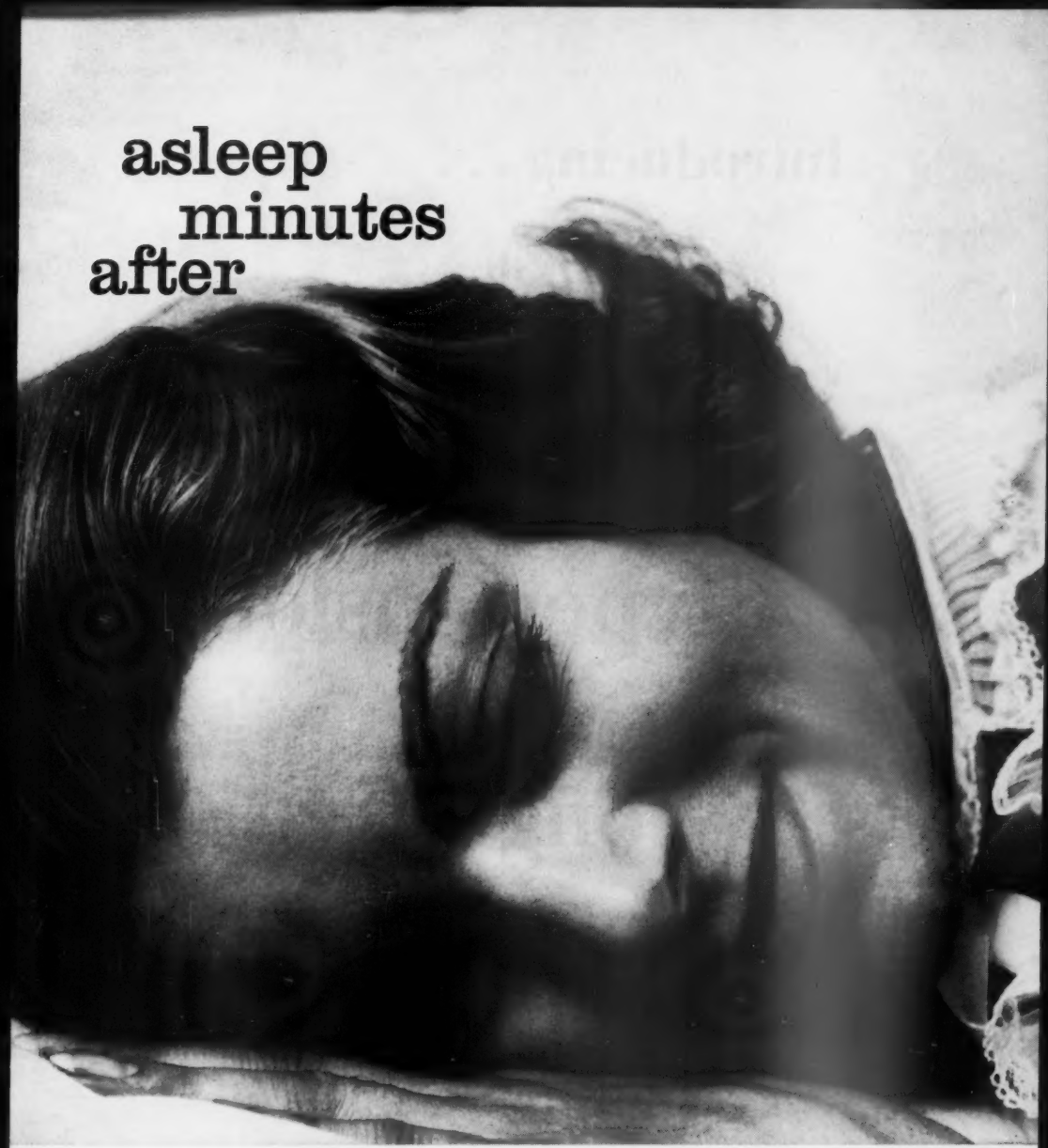

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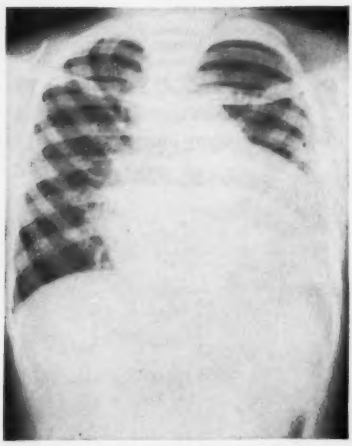

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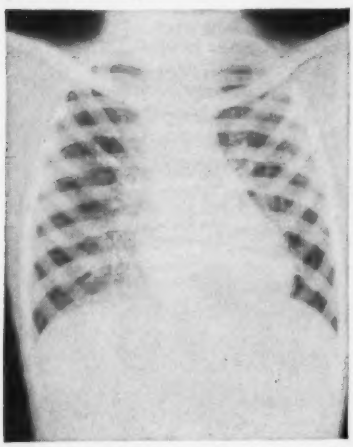

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1. Massell, B. F.: Paper presented at A Symposium on Steroid Therapy, Chicago, Ill., May 15-16, 1959.

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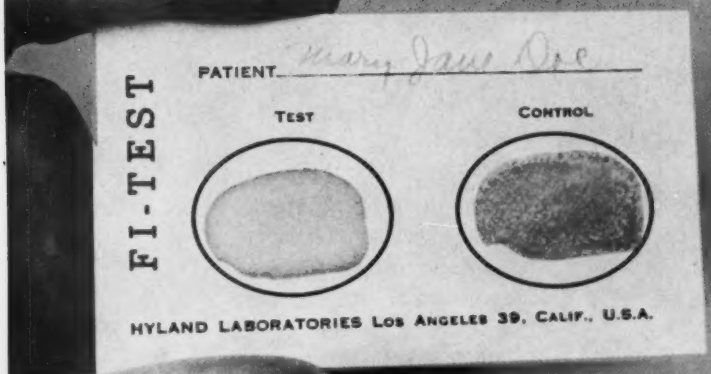

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1. Boer, S., et al.: J.A.M.A. 167:704, June 7, 1958.
2. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13.

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	2–6	9–13	16–20	23–27	Jan. 30–Feb. 3	9–10	13–27	20–24
Course No. 4, RECENT ADVANCES IN DRUG THERAPY: University of Washington School of Medicine, Seattle, Wash.; Robert H. Williams, M.D., F.A.C.P., Director.		X						
Course No. 5, MECHANISMS OF DISEASE: Columbia University College of Physicians and Surgeons, Presbyterian Hospital, New York, N. Y.; Alfred P. Fishman, M.D., F.A.C.P., and Stanley E. Bradley, M.D., F.A.C.P., Co-Directors.			X					
Course No. 6, SELECTED TOPICS IN INTERNAL MEDICINE: The University of Oklahoma School of Medicine and University Hospitals, Oklahoma City, Okla.; Stewart G. Wolf, Jr., M.D., F.A.C.P., and James F. Hammarsten, M.D., F.A.C.P., Co-Directors; William O. Smith, M.D., (Associate), Associate Director.								X

The following courses are scheduled for Spring, 1961: RECENT ADVANCES IN CARDIOVASCULAR DISEASE, Mount Sinai Hospital, Charles K. Friedberg, M.D., F.A.C.P., Director, March 6–10; INTERNAL MEDICINE: SELECTED TOPICS, McGill University, W. H. Philip Hill, M.D., F.A.C.P., Director, March 13–17; ADVANCED CLINICAL ELECTROCARDIOGRAPHY, The University of Tennessee, I. Frank Tullis, M.D., F.A.C.P., Director, March 20–24; ENDOCRINOLOGY AND METABOLISM, University of Virginia, William Parson, M.D., F.A.C.P., Director, March 23–25; PROBLEMS OF GROWTH AND AGING, Lankenau Medical Building, Philadelphia, Edward L. Bortz, M.D., F.A.C.P., Director, April 12–15; GASTROENTEROLOGY, University of Pennsylvania School of Medicine, Henry L. Bockus, M.D., F.A.C.P., Director, May 15–19; CURRENT ASPECTS OF INTERNAL MEDICINE, State University of Iowa, William B. Bean, M.D., F.A.C.P., Director, June 19–23.

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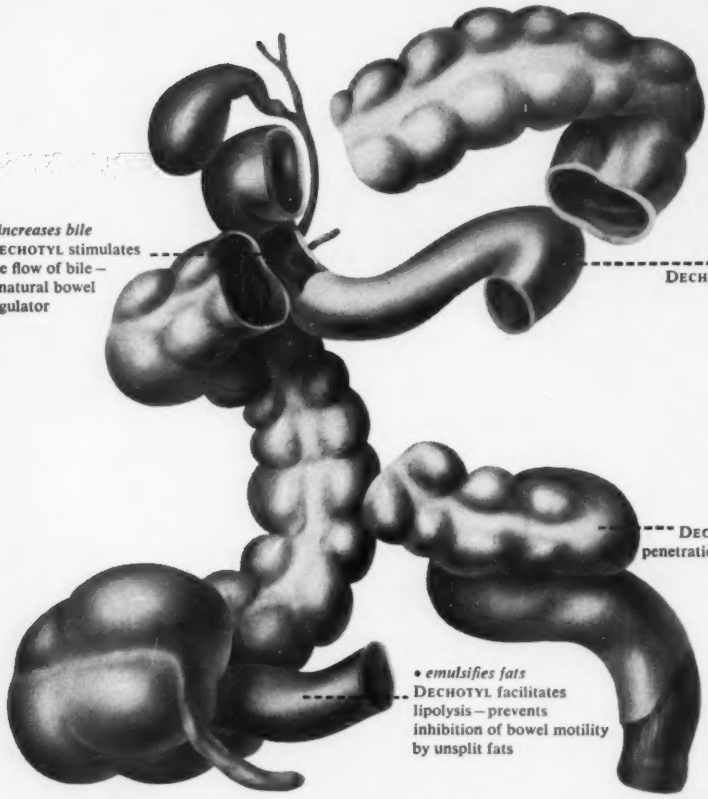
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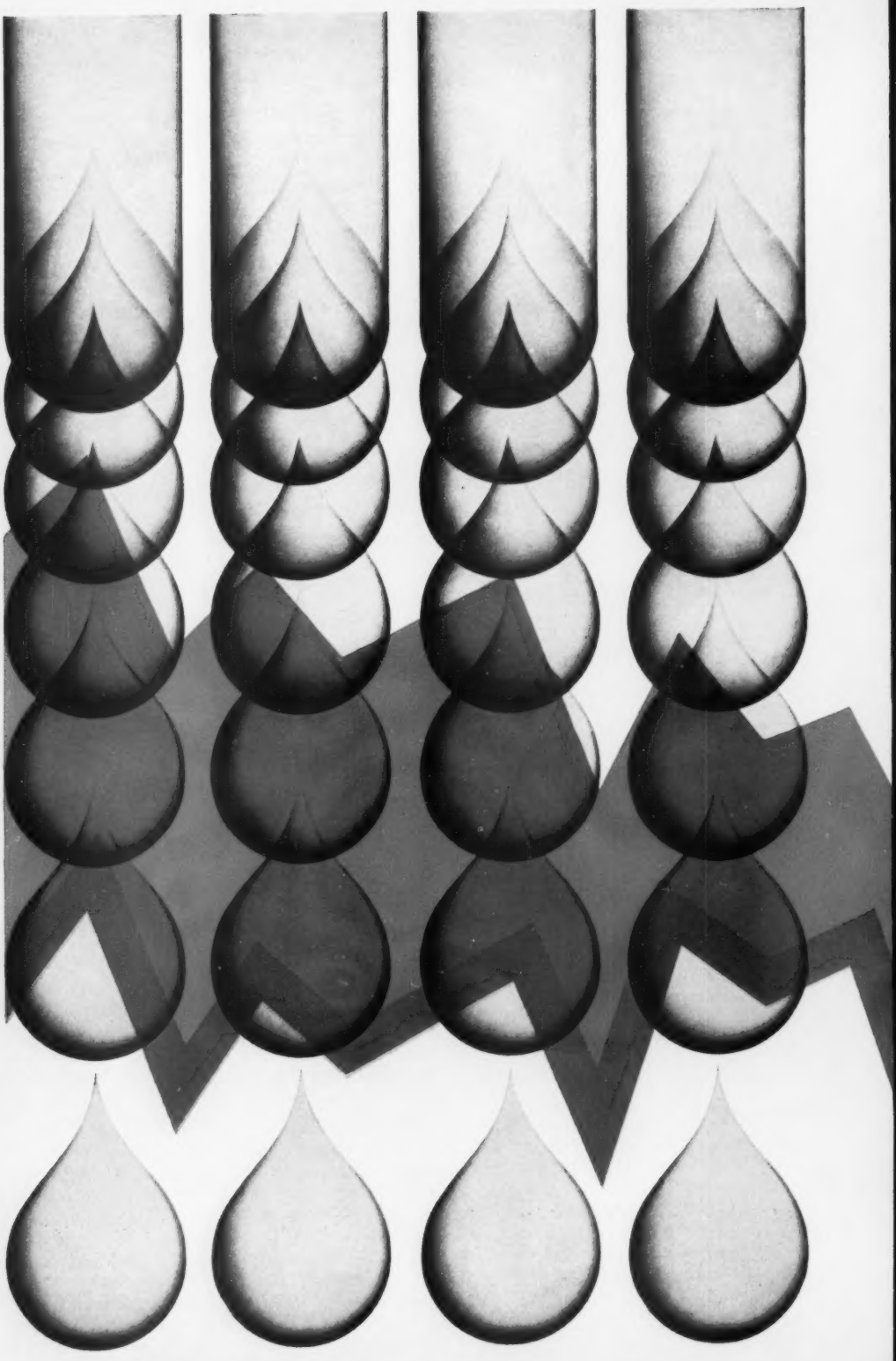

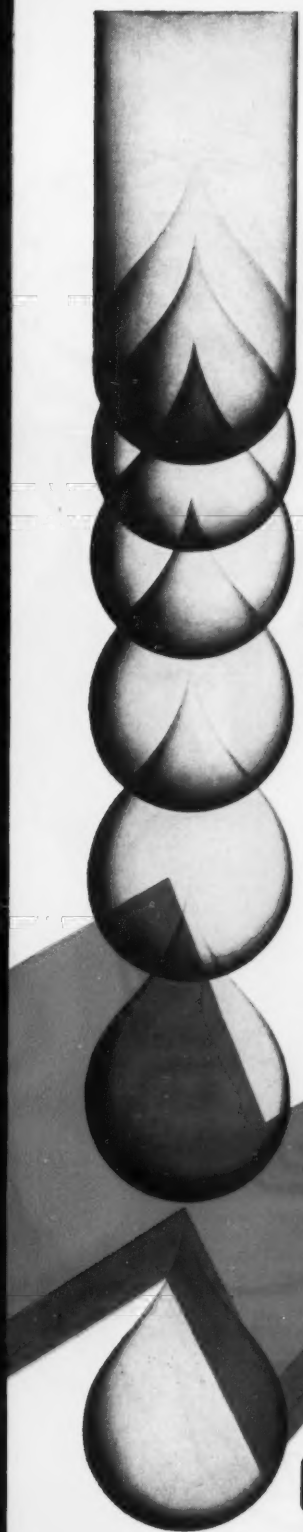

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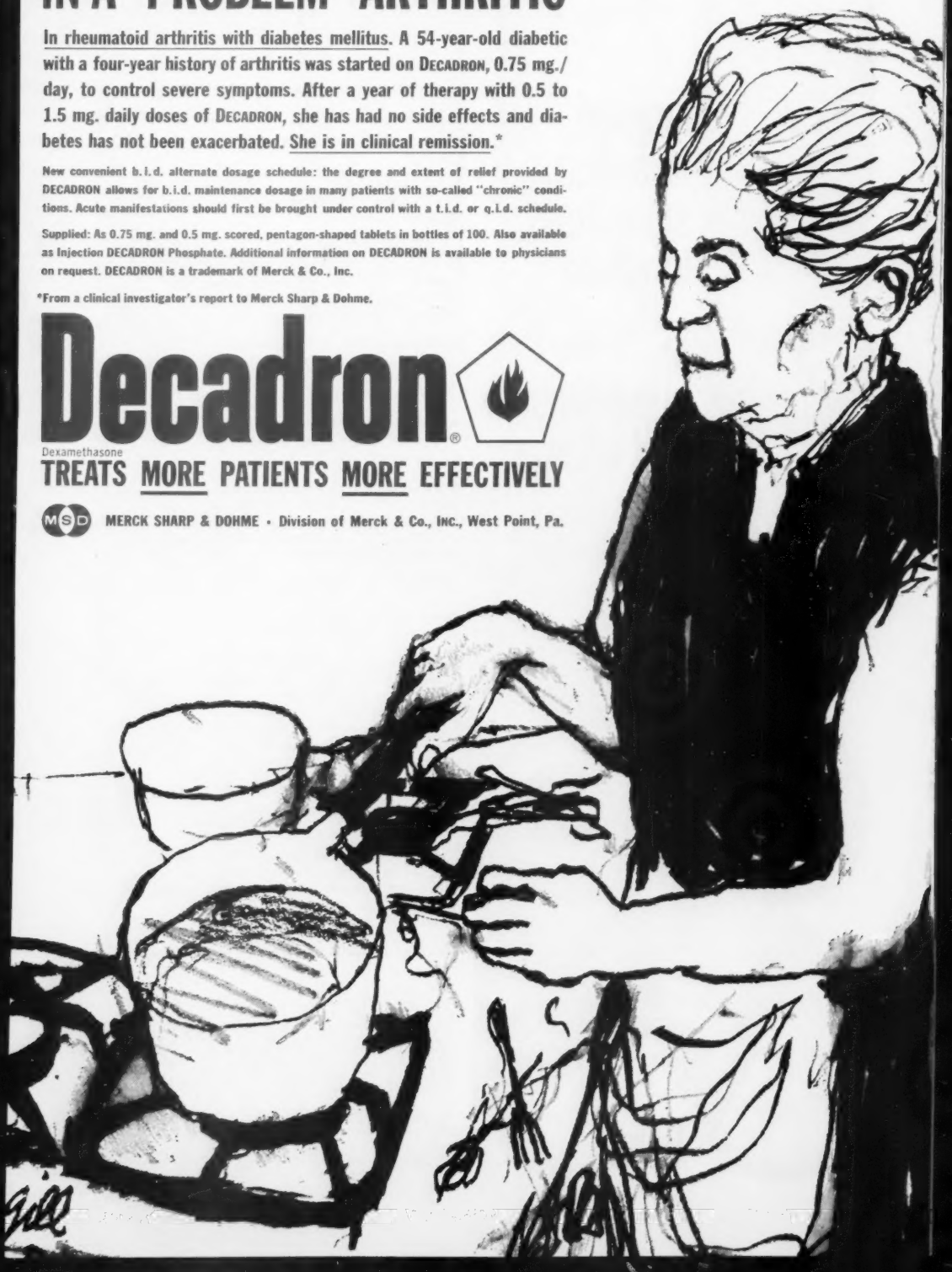

ANNALS OF
INTERNAL MEDICINE

VOLUME 53 DECEMBER 15, 1960 NUMBER 6

PULMONARY EMPHYSEMA: ETIOLOGIC FACTORS AND CLINICAL FORMS*

By DICKINSON W. RICHARDS, M. D., F.A.C.P., *New York, N. Y.*

RESEARCH during the last decade in the anatomic, physiologic and clinical features of pulmonary emphysema has brought, among other things, an increased interest in and need for a more satisfactory classification of this disease. But this is difficult. No one thus far has offered a convincing unitary hypothesis for the pathogenesis of emphysema, and the descriptions of the disease by the pathologists, physiologists and clinicians are still in somewhat different languages, and do not readily fit together. The disease itself is complex, so many different factors combining in such differing proportions, and so variably from one part of the lung to another.

But progress has certainly been made. There is on all sides an appreciation of the obvious fact that structure and function must be tied together; appreciation, also, that a physiologic description of the patient's disease, or an anatomic description, no matter how complete, will provide only a momentary view of the disease itself, and never the whole story of its course. The clinician also plays a role.

Among many important research achievements, two may be cited as having been of special influence in bringing physiologists and pathologists to study problems in common. One was the discovery by Gough and Wentworth[1] of a simple technic by which re-inflated whole lung could be sliced into thin sections and permanently fixed. By this means, all of the functioning organ could be reviewed, the parts most destroyed as well as those still working, and special sections chosen for study. The other

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Presented as the John Phillips Memorial Lecture at the Forty-first Annual Session of The American College of Physicians, San Francisco, California, April 5, 1960.
From the First Medical and Chest (Columbia University) Services, Bellevue Hospital; and the Department of Medicine, College of Physicians and Surgeons, New York, N. Y.
Requests for reprints should be addressed to Dickinson W. Richards, M.D., Director, First Medical Division, Bellevue Hospital, 462 First Avenue, New York 16, N. Y.

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contribution came from the physiologists, and this in successive stages: first, the general concept of the relation between ventilation and perfusion of the respiratory tissues, and the consequences of disturbance in these relations;[2, 3] and second, the mapping out of the extraordinarily different performances, in ventilation and in gas exchange, in different parts of the same lung.[4, 5, 6, 7, 8]

In the last decade, also, aided by physiologic and pathologic studies, the clinicians have worked out certain patterns in this disease: the natural history of emphysema in its various forms.

As an interval step, directed toward the objective of a combined description or classification of emphysema, it might be of interest to examine some of the major factors, or forces, which appear to be operative in producing the emphysematous state, and some of their consequences. This is the subject of the present paper.

Table 1 gives the three categories that I will discuss. The first is the classic, the very large group of pulmonary emphysemas intimately associated with chronic bronchial and bronchiolar infection—a large part of what the British include in their term, "chronic bronchitis." The second is that

TABLE 1

Chronic Pulmonary Emphysema

1. Chronic bronchitis and emphysema
2. Pulmonary fibrosis and emphysema
3. Bullous emphysema (primarily nonobstructive, "atrophic")

of pulmonary emphysema associated with a primary fibrosis, the pneumoconioses, various forms of tuberculosis, and the many other fibrosing diseases. These have been studied by investigators in various parts of the world, and I will refer to them only briefly. An excellent review is included in the monograph by Gilson and Hugh-Jones.[9] The third is an interesting category, only recently fully recognized, and still being assembled. It is less common than the others, but not uncommon, when one gathers together all its forms. Here, the initial event appears to be a breaking down of the finer lung tissues, a destructive process of unknown cause, with formation of bullae.[10, 11, 12]

It scarcely needs to be pointed out how frequently these factors coexist, one complicating the other, so that in the later stages of an individual case it may be impossible to determine which was the primary etiologic process.

The broad concept of chronic bronchitis as used in Great Britain—including both the local infection and the sequelae, such as emphysema, which result from it—has much to recommend it. For one thing, it shows how important this group of diseases is, causing as it does 10% of all absenteeism in industry in Britain, and a mortality, for example, in men between 45 and 65 years of age, equal to that of lung cancer, three times that of tuberculosis, eight times that of pneumonia.[13] For another, it emphasizes the role

of chronic infection in the etiology of obstructive emphysema, and while there is not so much chronic bronchitis in this country as in Britain, we have a great deal, and the more carefully we inquire into this, in individual cases, the more frequently we find evidence of it. Gaensler and Lindgren,[14] in a recent study of 555 cases of emphysema, found 68% with a definite history of chronic bronchitis, and 18% more who had developed productive cough after the onset of dyspnea.

Pathologists have varied greatly in the relative emphasis which they give to one or another of the numerous anatomic features of chronic bronchitis: enlarged glandular cells in the smaller bronchi, with hypersecretion; thickened walls or mucous membranes, mucus and pus in the lumen, fibrosis, small abscesses, obliterated bronchioles alternating with dilated ones, kinked or flattened or slantingly inserted bronchioles, or actual check valve mechanisms—all of these may occur in varying proportions in different cases.[15, 16, 17] Obstruction is an essential and almost inevitable feature of such alterations in the finely constructed bronchial tree.

The more the finer air passages are involved, moreover, the more likely the development of obstructive emphysema. The characteristic dilatation in chronic diffuse vesicular emphysema, according to Heppleston,[18] involves particularly the terminal alveolar ducts and alveoli. It is often difficult to determine, at any particular emphysematous locus, whether the chief pathogenic force has been dilatation due to air trapping behind a narrowed bronchiole, dilatation secondary to an adjoining fibrosis or atelectasis, or dilatation due to actual injury and weakening of the involved pulmonary tissues themselves. All combinations and degrees of dilatation and destruction may exist, within the same lung as well as from one lung to another, the progressive attenuation and loss of substance of alveoli and air passages extending at times to the formation of large bullae, with multiple bronchial openings. Variable amounts of fibrous and muscle tissue, of septal or bronchial or vascular origin, are included in these emphysematous structures. The characteristic relative ease of inspiration and progressive hindrance to expiration in chronic bronchitis with emphysema indicate that the air passages can still alter their size; and, in general, the partial reversibility of the obstruction with treatment also demonstrates that much of the anatomic change remains nonrigid, for one reason or another.

A recent pathologic finding of importance, revealed by the Gough technic of whole lung section, is the "centrilobular" dilatation of smaller air passages in diffuse emphysema.[19] Whether this is caused by local inflammation, weakening, and destruction of tissues, or by mechanical forces inducing dilatation, and strongest at these locations, has not yet been determined.

It should be noted that there are forms of bronchitis, with very tenacious sputum in the smaller bronchi, in which emphysema may be slight or even absent; yet the process may be so severe that the patient will die in ventila-

tory failure and asphyxia, in spite of bronchoscopic suction, tracheotomy, and the use of respirators.[20]

With this rather bewildering diversity of anatomic change, one might expect that clinically and physiologically also, chronic bronchitis and emphysema would present a picture equally or even more chaotic in its manifestations. Actually, while there are many variations from one case to another, one can discern two general patterns, one or the other of which will usually dominate the scene.

In both forms there will be a similar long history of chronic cough, aggravation during respiratory infections, and gradual progression to obstructive dyspnea, more or less disabling. The amount of cough, or of sputum, and the presence of asthmatic breathing, at least in the histories of our patients at Bellevue Hospital, have been quite variable.

From this common background the two groups diverge: one shows predominantly obstructive emphysema with ventilatory insufficiency, the other, predominantly the syndrome of alveolar hypoventilation.

In the first, the clinical picture is dominated by obstructive dyspnea, the chest is hyperinflated, physical and radiologic evidences of emphysema are manifest, and there is hyperpnea at rest and in exercise. As the disease progresses, often over many years, dyspnea becomes more and more extreme, until the least effort, such as dressing or talking, becomes difficult. With acute respiratory infection, symptoms are worse, and at these times there may develop a marked hypoxia, hypercapnia and cor pulmonale. In the intervals, however, hypoxia and hypercapnia are not prominent features.

Physiologically, the ventilatory evidences of emphysema are classic: large residual volume, progressive expiratory obstruction, often with air trapping, greatly diminished breathing capacity, and greatly increased work of breathing. Distribution of inhaled air, according to the technics of Briscoe, shows marked unevenness, but there remains enough ventilation of still perfused lung tissue so that, as already indicated, CO_2 is effectively handled, and arterial hypoxia slight or moderate. Hyperventilation, at rest and in exercise, persists throughout the course of the disease.

At autopsy, these cases have manifest structural emphysema and large lungs, typically the "hypertrophic" emphysema. The degree of chronic bronchitis itself may be severe or relatively mild. In fact, in many instances the question may well be raised whether there is not also an element of "atrophic" emphysema present. This will be referred to again later.

In the original physiologic classification of Baldwin, Cournand, and Richards,[21] these cases would fall into Groups I and II. The new and significant fact is that they appear to run their whole clinical course here, without moving into Groups III and IV, except transiently or terminally, in some instances, when complicated by acute infection.

It might be noted at this point that, in our view, this form of emphysema, with profound disability caused by ventilatory inadequacy, is very much to

be included in the category of "pulmonary insufficiency"; or, to put the argument the other way about, the term "pulmonary insufficiency" should not be restricted to cases with defective respiratory gas exchange, involving marked arterial hypoxia or hypercapnea.

The second group, the patients with chronic bronchitis and emphysema complicated by alveolar hypoventilation, are seen, at least in our Clinic, much less frequently than those with predominantly ventilatory insufficiency. In this second group, after a history of a variable number of years of chronic cough and increasing obstructive dyspnea, cyanosis appears, with a tendency to polycythemia, right heart hypertrophy, and failure. With adequate treatment of the pulmonary condition, hypoxia is relieved, polycythemia disappears, and cardiac compensation is restored. The same picture of cardiopulmonary failure recurs with each serious exacerbation of the primary disease, the whole course of this phase of the disease extending sometimes for 10 or even 15 years, provided adequate treatment can be given during acute exacerbations.

Physiologic manifestations are in some respects constant, in others variable from one case to another. There is always air-passage obstruction, though this may be remarkably relieved during adequate therapy. Vital capacity may be only moderately diminished, and maximal breathing capacity is at some stages moderately, at others markedly decreased. The spirogram is emphysematous in form, residual volume often not greatly increased.

The striking and constant physiologic finding is the profoundly disturbed ventilation/perfusion relationship. As shown by the technic of foreign gas inhalation, or by nitrogen washout by breathing oxygen, large pulmonary volumes are poorly ventilated, only about 10% of the volume adequately or even overventilated.[5, 6] The cyanosis arises from the fact that 90% of the lung is obstructed or underventilated in relation to its volume. Furthermore, the less ventilated alveoli are not particularly underperfused. (This contrasts with the preceding group, in which about 70% of the lung is both underventilated and underperfused.) Thus, almost all of the blood is being oxygenated in a part of the lung the ventilation of which varies critically with the degree of bronchitis and obstruction. Diminished pulmonary ventilation, caused in part by diminished respiratory stimulus, compounds the insufficiency.

Whether in these cases there is also a true failure of diffusion, caused by attenuated alveoli with inadequate diffusing surface,[3a, 3b, 22, 23] cannot be certainly ascertained. The argument in favor of such a hypothesis has been considerably weakened by Briscoe's analysis, since it is no longer needed.[8] The latter's reasoning, in its simplest terms, is as follows: One can imagine two perfectly normal lungs, one being ventilated but not perfused, the other perfused but not ventilated. The "diffusing capacity" of such a system would be zero. Suitable variations in ventilation/perfusion relations could thus give a variety of "diffusion" disturbances. The alteration in "diffusion

capacity," as a patient improves clinically, such as is seen not infrequently, would fit better with the ventilation/perfusion than with the diffusion hypothesis.

The physiologic description of the cardiovascular dysfunction in these cases has been fairly well worked out.[24] The arterial hypoxia is associated with a considerable pulmonary arterial hypertension, also in many instances with a gradually developing polycythemia and increased blood volume. The latter overfills the blood bed and the heart, sometimes increases cardiac output, and further aggravates the pulmonary hypertension, all of which put added strain on the right ventricle, which eventually fails. With relief of hypoxia, when the pulmonary disease is adequately treated, the pulmonary arterial pressure drops and frequently returns to normal.

The pathology in these cases of chronic bronchitis with emphysema and alveolar hypoventilation is interesting in that it is so different from one case to another. In some there may be an intense chronic and subacute bron-

TABLE 2

Chronic Bronchitis and Emphysema
Ventilatory Insufficiency versus Alveolar Hypoventilation

Patient	W. D.	M. K.	Predicted Normal
Anatomic emphysema	Marked	Mild	—
Ventilatory insufficiency	Severe	Severe	—
Max. breathing capacity, L./min.	17	24	150
Ventilation, L./min./sq. m. B.S.			
Rest	4.7	3.5	3.1
Exercise	16.0	6.6	10.0
Alveolar hypoventilation	Slight	Severe	None
Arterial O_2 saturation, %			
Rest	94	76	96
Exercise	84	68	96
Arterial pCO_2, mm. Hg	35	72	40
Cor pulmonale	None	Failure	—

chitis, with all the anatomic changes of advanced obstructive emphysema, including at times large bulla formation; in others, only the mildest changes of pulmonary emphysema are found; and there are all stages between. Baldwin, Cournand, and Richards called attention to these cases of profound ventilation/perfusion dysfunction with only minor alveolar damage,[21] and recently Ogilvie has described similar cases.[25] There is no plausible hypothesis as yet as to why these patients, with such slight anatomic changes, should suffer such profound and even lethal physiologic disturbance—unless one might suppose that the hypoxic reflex, closing off pulmonary blood flow in nonventilated regions, as postulated by Liljestrand,[26] is no longer functioning.

Table 2 gives some contrasting figures in physiologic function in a case of ventilatory insufficiency and a case of alveolar hypoventilation.

Table 3 presents, in outline form, the categories of "chronic bronchitis" which we have just described.

TABLE 3

Chronic Bronchitis and Emphysema
Clinical Forms

1. Chronic infection: (a) mild to moderate, with sputum
   (b) severe, with tenacious sputum, obstruction, asphyxia
2. With diffuse obstructive emphysema
   (a) Ventilatory insufficiency. Hyperpnea, some hypoxia, no hypercapnia. Cor pulmonale: none or only terminal.
   (b) Alveolar hypoventilation. Combined ventilatory insufficiency with severe ventilation/perfusion disturbance, hypoxia and hypercapnia. Cor pulmonale: early, and recurrent or continued.

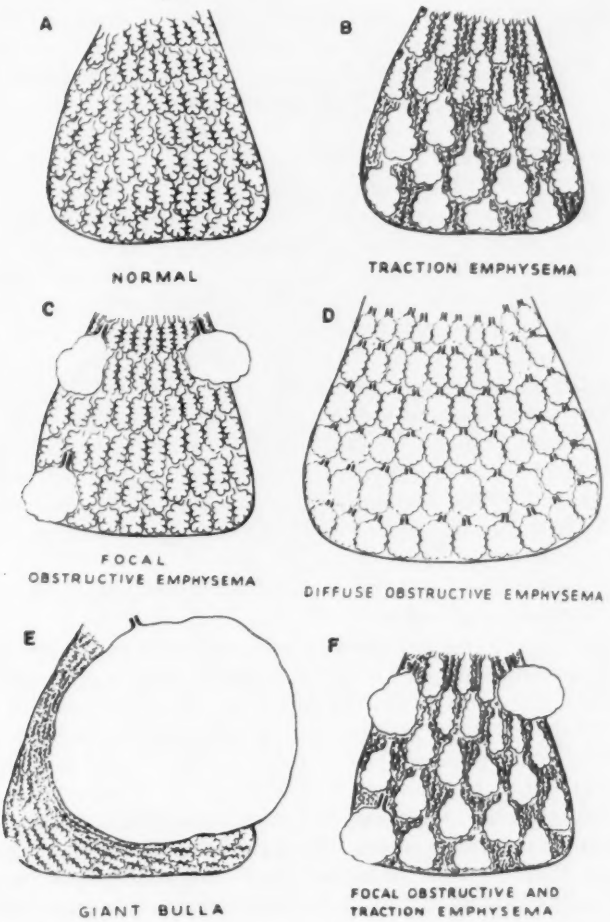

FIG. 1. Schematic diagram of anatomic forms of pulmonary emphysema, as presented by Liebow. (Courtesy Liebow, A. A.: Vascular pathology of pulmonary emphysema, Am. Rev. Resp. Dis. **80** (Suppl.): 67, 1959.)

The category of "emphysema and pulmonary fibrosis" is obviously a very broad one, with extension into almost every kind of chronic pulmonary disease. The schematic diagram of Liebow,[16] as shown in figure 1, describes the two most frequent pathogenetic factors in the development of the overdilated, emphysematous state of respiratory tissues, traction emphysema from fibrosis with shrinkage, and obstruction. The so-called "honeycomb lung" is often secondary to an interstitial fibrosis, with traction emphysema.[27] In the typical pneumoconiosis of coal miners, Heppleston[28] describes the first-order respiratory bronchioles running through "cylinders of dust," with eventually the formation of starshaped foci of fibrosis that dilate and distort these air passages. When these cases develop diffuse emphysema, there is physiologic evidence of air passage obstruction hard to distinguish from that of bronchitis with emphysema; and indeed, at this stage, there is usually a considerable degree of secondary infection and true obstruction. The natural history of an old case of pneumoconiosis with obstructive emphysema is essentially the same as that of old chronic bronchitis: years of increasing dyspnea and cough, with or without asthma; and the relentless progress through ventilatory insufficiency, sometimes with alveolar hypoventilation and cor pulmonale, is also the same. Figure 2 shows the Gough section on such a patient, whom we followed for a number of years. This patient had also considerable bronchitis, recurring pneumonia, and physiologically all the evidence of obstructive and restrictive ventilatory insufficiency and alveolar hypoventilation. His last years were a losing struggle, with repeated courses in the Drinker respirator. The section shows well the massive fibrosis, and the tendency, in both the large and small fibrotic areas, for stellate shrinkage of tissue toward the fibrotic centers. Figure 3, for comparison, is the Gough section of the lung of a patient who had a longstanding chronic bronchitis and emphysema with alveolar hypoventilation. Anatomically, it is a good example of centrilobular emphysema.

This is as much as I can say, in this brief outline, about this large and important form of emphysema.

The third part of this discussion is concerned with a class of emphysema associated especially with the formation of bullae—that is, gross enlargement of pulmonary air spaces caused by distention and breakdown of bronchoalveolar substance, with preservation of anatomic connection with the tracheobronchial air passages. It is suggested that "bulla" is a better name for this lesion than is "air cyst." The lesion is almost always multiple, more or less irregular in contour, and contains within it shaggy strands of residual fibrous or muscle tissue. By derivation, "cyst" was the name for the urinary bladder. The term "air cyst" might therefore be restricted to the designation of air sacs of single and uniform contour, especially those with definite epithelial lining.

Interest in large air-containing lesions in the lung, variously termed

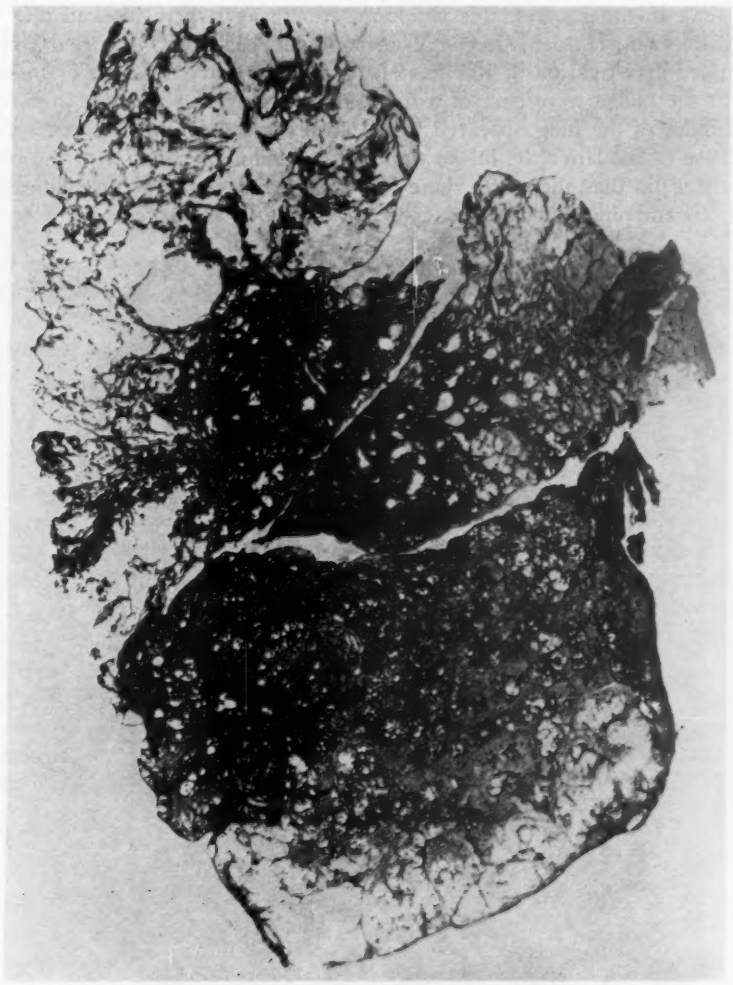

FIG. 2. Gough section of patient with advanced pulmonary fibrosis and emphysema, chronic bronchitis, severe ventilatory insufficiency, and recurrent alveolar hypoventilation. See text.

"blebs," cysts," "congenital cysts," "air cysts" or "bullae," was stimulated by the technic of bronchospirometry,[29] and much more by the advances in thoracic surgery, when it became possible to excise these large, space-filling structures, with clinical benefit.[30, 31] In 1939 Kaltreider and Fray[32] carried out physiologic studies demonstrating that, in some instances, there appeared to be free communication between the bullae and the bronchial tree,

but that, in other cases, this communication was largely blocked off. In 1950 Baldwin, Harden, Greene, Cournand, and Richards[33] reported a more extended investigation in 16 cases of "large pulmonary air cysts or bullae." In 10 the bullae were part of a diffuse pulmonary emphysema; in six the remainder of the lung appeared to be physiologically normal, or nearly so. In three of the latter the bullae were in free communication with the bronchial tree; in the other three there was poor or intermittent communication, with air trapping and "tension cyst" formation. Of the three with openly

FIG. 3. Gough section of patient with chronic bronchitis and emphysema, severe ventilatory insufficiency and alveolar hypoventilation. There are numerous areas of centrilobular emphysema.

communicating lesions, one was a chronically infected condition that had existed since infancy, the other two consisted of large bullae, first noted at the ages of 31 and 39, respectively. Physiologically, these patients had increased residual lung volumes, slightly diminished maximal breathing capacities, some hyperpnea on exercise, and otherwise normal pulmonary function. No consideration was given in this paper to the possible pathogenesis of this type of nonobstructive bullous lesion.

Subsequent study has revealed that this is a not uncommon condition, with a fairly characteristic natural history. A relatively young individual, with no symptoms and no history of infection, is found to have large bullae in his lungs by x-ray. These usually extend slowly and progressively, but the patient may continue for years without symptoms.

Belcher and Siddons[10] have described this disease; so, more recently, have Ogilvie and Catterall.[12]

Laurenzi, Turino, and Fishman[34] have completed a study including five such cases, and I am privileged to quote from the details of their work, thus far published only in abstract form.

Physiologically, these patients had normal vital capacities and maximal breathing capacities, but their chests were held in the inspiratory position, giving them large expiratory reserve volumes. The nitrogen washout, the index of intrapulmonary mixing, was variable from one test to another, suggesting that the bullae were sometimes well ventilated, sometimes not. Blood gases, pulmonary blood flow, and the patients' exercise capacities were normal.

Pulmonary compliance in these early cases—that is, the ease of inflation and deflation of the lung—was actually greater than normal, indicating again the complete absence of obstruction or of diffuse fibrosis. This is illustrated in figure 4, and in the x-ray of the patient from whom this record was taken, in figure 5.

The entire picture suggests that, except for the bullous degeneration, there is a large amount of functionally normal lung, and this is in fact what is demonstrated in early cases that have come to surgery or autopsy. These bullae, however, are rarely "solitary," and close study, even in early cases, will show multiple involvement of the lung.

The essential lesion appears to be a dissolution, a cell death or disappearance, without inflammation, of the alveolar and finer respiratory structures, leaving bullae of varying sizes, their cavities crossed by radiating strands of residual septal tissue or smooth muscle. The pathogenesis is obscure. Some have had a history of pneumonia in earlier life, but others have not. The force enlarging these bullae appears to be the elastic contraction of the normal lung, pulling apart the flaccid degenerated tissue. We have termed the pathogenetic process here "atrophic," realizing the vagueness of this term, and also the likelihood that a better and more positive description will eventually be worked out.

If one can accept the proposition that nonobstructive bullous emphysema is a more or less independent disease, then the natural variations in extent and progression of the disease will come to include a fairly wide variety of clinical conditions.

In the functionally normal cases, symptoms are not infrequently ushered in by an acute, spontaneous pneumothorax. The most common history is that of slow progression of the disease, with enlargement of existing bullae and formation of others, over periods of five to 10 years; but in some cases

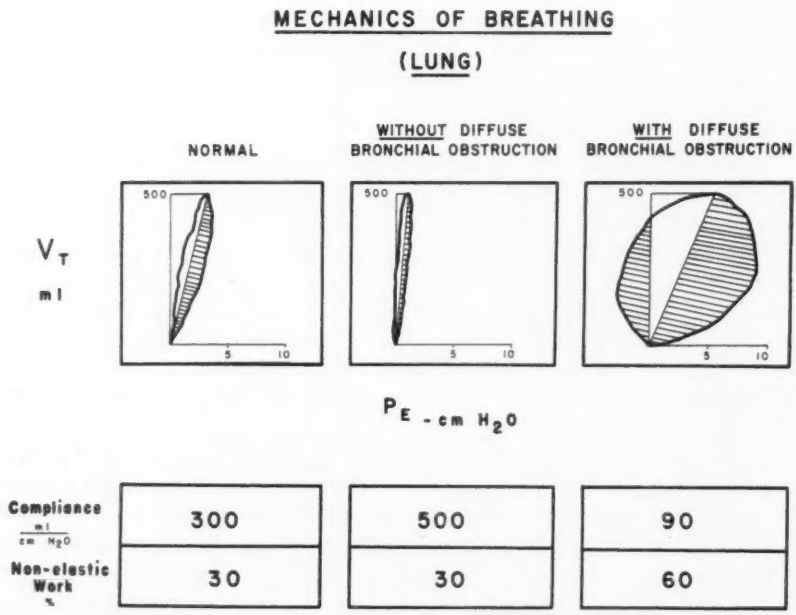

FIG. 4. Mechanics of breathing in a normal subject, a patient with nonobstructive bullous emphysema, and a patient with obstructive emphysema. Volume-pressure diagrams show the pulmonary compliance (steepness of the curve) in a normal subject, a patient with nonobstructive bullous emphysema, and a patient with obstructive emphysema. V_T = tidal volume of respired air. P_E - cm H_2O = negative pressure, in cm. of H_2O. Righthand curve in each box is the pressure inscribed during inspiration; lefthand curve, the pressure during expiration. (Courtesy Laurenzi, Turino, and Fishman.)

the disease advances more rapidly, and in others even more slowly. If there is recurrent infection the deterioration is faster, but the disease will progress without apparent infection.

Symptoms are caused by the progressive loss of functioning pulmonary tissue, and this includes both the tissue actually destroyed and that which has become shrunken and atelectatic, contracting away from the bullous degeneration. These symptoms are progressing exertional dyspnea and frequently an attending fatigue and weakness. Physiologically, as one would expect, the picture is that of ventilatory insufficiency. Vital capacity

and maximal breathing capacity are diminished. There are usually hyperpnea associated with increased dead-space ventilation, and in general a marked ventilation/perfusion derangement. Arterial hypoxia and hypercapnia are late developments, as is cor pulmonale. Oxygen therapy or respirators will be needed in the final stages.

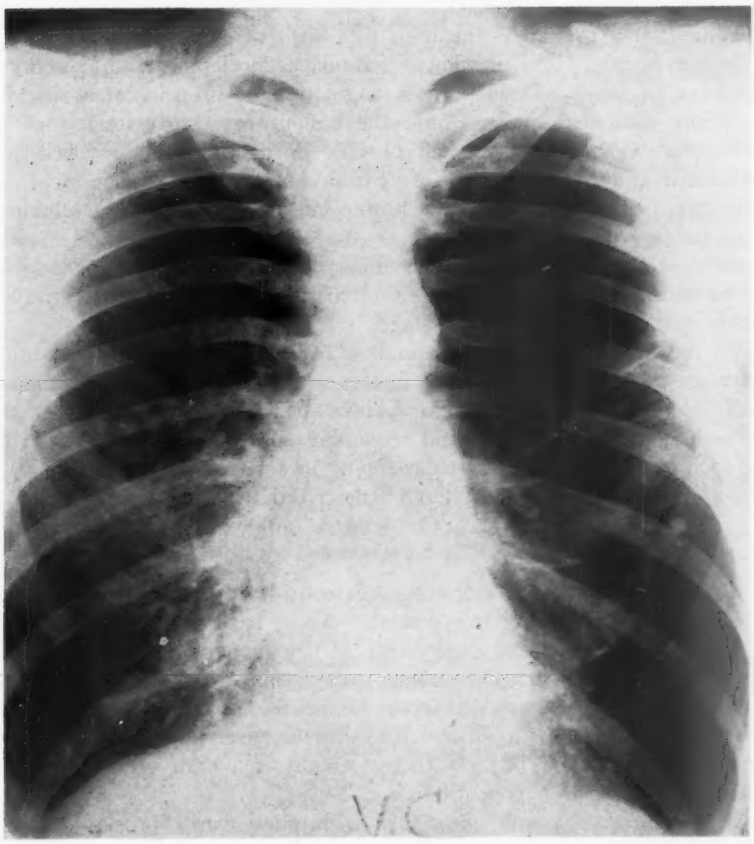

FIG. 5. Chest x-ray of patient with nonobstructive bullous emphysema and increased pulmonary compliance (see middle chart in figure 4). The patient had no symptoms, and had normal exercise capacity. See text.

At any time in the course, recurring or chronic infection may become an added and often serious complication, contributing especially to the factor of obstruction, but also to pulmonary dysfunction generally. As in the case of bullae in chronic bronchitis and emphysema, one or more of the bullae themselves may become infected and filled with fluid. These usually respond to medical therapy and empty again without surgical drainage. In a case

of long standing, complicated by infection, it is often impossible to determine whether it originated as chronic bronchitis or as atrophic bullous emphysema.

Infrequently, the disease will be widely disseminated throughout the lungs at a relatively early stage, with early and severe ventilatory insufficiency. Such cases can be recognized only if they remain free, or nearly free, of bronchitis; and are more likely to be encountered in private practice than in the clinic.

While not a primary element in this form of emphysema, obstruction of the air passages is a prominent secondary development, and occurs in a number of ways. Distortion or angulation of bronchiolar walls, flap formation, slantwise entrance into the bullous cavities, softening of the bronchiolar walls themselves, all provide opportunity for a check-valve mechanism and the formation of tension bullae, with displacement and compression of adjoining lung. Chronic infection adds to the mechanisms of air passage obstruction. These are the lesions whose surgical excision provides such striking clinical benefit, especially if compressed good lung can be released and reëxpanded. Obstructed bullae are almost always a feature of the disease in its later stages.

At the far end of the spectrum is a condition or group of conditions which are probably distinct, and probably not to be classified as emphysema at all. These are the true "solitary" bullae, or air cysts, with the remainder of the lung perfectly normal and remaining so. Baldwin et al. described one such case, a single air cyst developing in a young person after a pneumonia;[21] and Ogilvie and Catterall[12] described two cases.

Summary

1. Chronic pulmonary emphysema is considered in terms of the major etiologic forces producing this disease. Three basic forms are described: (a) chronic bronchitis and emphysema, (b) pulmonary fibrosis and emphysema, and (c) nonobstructive bullous emphysema.

2. Within the category of chronic bronchitis and emphysema, two chief clinical forms can be distinguished: (a) obstructive emphysema with ventilatory insufficiency, and (b) obstructive emphysema with ventilatory insufficiency and alveolar hypoventilation.

3. In the emphysema associated with pulmonary fibrosis, the basic etiologic forces are: (a) traction, and (b) obstruction.

4. The class of primarily nonobstructive bullous emphysema is presented as a disease in which the etiologic factor is an essential destruction or "atrophy" of respiratory tissues. Secondary air passage obstruction, however, occurs from various mechanical causes, and is an important and almost inevitable complication in this disease.

Acknowledgments

The author expresses his special thanks and appreciation to Dr. John B. Cromie for permission to publish reproductions of two specimens from his collection of Gough sections;

and to Dr. Gustav A. Laurenzi, Dr. Gerard M. Turino and Dr. Alfred P. Fishman, for permission to quote from their forthcoming paper on bullous emphysema.

SUMMARIO IN INTERLINGUA

In le presente reporto, emphysema pulmonar es considerate in tres categorias: (1) Chronic bronchitis e emphysema, (2) fibrosis pulmonar e emphysema, e (3) emphysema bullose—primarimente non-obstructive, "atrophic."

Ab le puncto de vista clinic, le plus grande del gruppos—illo de chronic bronchitis e emphysema—pare includer duo formas general, i.e. (a) emphysema obstructive con insufficientia primarimente ventilatori, in que dyspnea obstructive es le symptoma major e in que hypoxia, hypercapnea, e corde pulmonal occurre solo tardive- o terminalmente, e (b) multo minus commun, emphysema obstructive con insufficientia ventilatori de longe durantia e le symptoma associate de hypoventilation alveolar. In casos de iste ultime forma, non solmente hypoxia arterial e hypercapnea sed etiam polycythemia, hypervolemia, e corde pulmonal es apte a occurrer precocemente e a persister durante un longe curso.

Alteration emphysematose in le varie formas de fibrosis pulmonar occurre principalmente como resultato de un obstruction del vias aeree o como dilatation secundari a un adjacente fibrosis con constringimento (emphysema de traction). Usualmente, un infection occurre como complication del tableau le qual—in le curso del tempore—pote devenir indistinguibile in terminos clinic ab illo de bronchitis chronic e emphysema.

Le tertie categoria—illo de un apparentemente primari "atrophia" con perdita de substantia pulmonar e sin obstruction del vias aeree—es un categoria plus o minus nove. Le pathologia characteristic in illo es le formation de multiple micre e grande bullas in regiones local del pulmon, con altere locos remanente in stato normal. Iste patientes subsiste frequentemente sin symptomas durante periodos de plure annos, sed finalmente illes suffre crescente grados de dyspnea e fatiga in tanto que le morbo progrede e que insufficientia ventilatori se disveloppa. Obstruction secundari del vias aeree—con o sin le formation de bullas de tension—es un complication quasi inevitabile que va supervenir precocemente o tardivemente in le curso del maladia.

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ABNORMALITIES OF PULMONARY GAS EXCHANGE IN OBESITY * †

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In 1955 a clinical "syndrome" was described that consisted of extreme obesity, hypoventilation, arterial hypoxia, polycythemia, and right heart failure.[1] Since then the physiologic mechanisms by which obesity could interfere with cardiorespiratory function have been under study.[2-17] Most reports have dealt with obese patients showing clinical evidence of dysfunction, and who were, therefore, probably in an advanced stage of the disorder. In an effort to elucidate the sequence of events that ultimately lead to the development in the obese of the so-called "pickwickian syndrome," we set out to study a group of subjects selected solely because of their marked obesity.

The findings appear to be somewhat at variance with the concept that hypoventilation is always the primary physiologic defect leading to a sequence of other disorders of function.[18] Whereas evidence of hypoventilation was present in some of our subjects, a more common abnormality was that of disturbed ventilation-perfusion relationships. This would seem to explain the presence, in some cases, of arterial hypoxia without CO_2 retention. Possible causes of this abnormality in the obese are discussed.

Methods

Twenty obese subjects were studied. Those whose history suggested cardiac or pulmonary disease were excluded. Physical characteristics of the subjects are shown in table 1. The mean age was 48 years; the mean height, 166 cm.; the mean weight, 142 Kg.; the mean body surface area, 2.37 M^2.

Studies were done under resting but not basal conditions. Gas exchange studies were performed in the recumbent position, and in five subjects were repeated in the sitting position.

The vital capacity and one-second forced expired volume were measured with a Stead-Wells respirometer.‡ Arterial blood was drawn from the brachial or radial artery using an indwelling Riley or Cournand needle and was analyzed for O_2 and CO_2 tension by the modified bubble equilibration method of Riley et al.[19] Arterial blood pH was measured in a closed Cambridge glass electrode at 37° C. In 16 subjects, expired gas was simul-

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taneously collected in a recording Tissot respirometer and was analyzed for O_2 and CO_2 in a Scholander micro-analyzer.

The "effective" alveolar oxygen tension ($P_{A_{O_2}}$) was calculated from the inspired oxygen tension ($P_{I_{O_2}}$), alveolar (or arterial) CO_2 tension ($P_{a_{CO_2}}$), and the CO_2–O_2 exchange ratio (R):

$$P_{A_{O_2}} = P_{I_{O_2}} - \frac{P_{a_{CO_2}}}{R} + \frac{P_{a_{CO_2}}}{R} F_{I_{O_2}}(1 - R).$$

TABLE 1
Physical Characteristics of Obese Subjects

Case	Sex	Age	Height	Weight	Body Surface Area
		Yr.	Cm.	Kg.	M.²
1	F	35	160	216	2.8
2	F	44	165	145	2.4
3	M	37	183	155	2.66
4	F	64	157	141	2.3
5	F	48	162	142	2.35
6	F	56	160	205	2.73
7	F	52	146	94	1.83
8	F	25	169	137	2.39
9	M	41	175	116	2.29
10	F	42	163	164	2.5
11	M	58	188	198	3.01
12	F	53	164	121	2.22
13	F	49	163	98	2.02
14	F	49	143	96	1.82
15	M	71	163	88	1.93
16	F	36	166	128	2.29
17	F	46	170	205	2.86
18	F	56	158	110	2.07
19	M	42	179	138	2.48
20	M	62	180	130	2.44

Physiologic dead space (V_D) was calculated from the arterial and expired CO_2 tension ($P_{a_{CO_2}}$, $P_{E_{CO_2}}$) and the tidal volume (V_T) according to the Bohr equation:

$$V_D = \frac{P_{a_{CO_2}} - P_{E_{CO_2}}}{P_{a_{CO_2}}} \times V_T.$$

The figure was corrected for the apparatus dead space. The venous admixture ratio, related to the cardiac output ($\dot{Q}va/\dot{Q}t \times 100$), was estimated from the charts prepared by Riley et al.[20] Pulmonary diffusing capacity was measured for O_2 [20] in seven cases and for CO in three, using the steady state, physiologic dead space method,[21] and the breath holding method.[22]

RESULTS

I. Ventilation: Ventilatory data are shown in table 2. They included vital capacity, one-second forced expiratory volume, frequency of respiration (f), and tidal volume (V_T). The mean vital capacity was 89% of that

TABLE 2

Ventilatory Data in Obese Subjects

Case	Vital Capacity		One-Second Forced Expiratory Volume		f‡	V_T§
	Ml.*	% of Pred.†	Ml.*	% of V.C.	Breaths/min.	Ml.*
1	2,250	77	1,870	83	36.5	294
2	1,680	58	1,440	86	30	459
3	2,320	54	1,970	85		
4	1,760	70	1,560	89	25	588
5	2,320	84			19	386
6	2,640	102	2,140	81	40.5	194
7	2,320	96	1,980	85	14	508
8	4,110	129	3,240	79	13	350
9	4,940	122	3,480	70	19	484
10	2,710	94			18	506
11	4,600	116	3,120	68	18	962
12	3,330	123	2,570	77		
13	2,280	83	1,890	83	12.5	438
14	1,920	79	1,760	92	20	295
15	2,220	69	1,770	80		
16	2,920	97	2,400	82	20	475
18	1,550	61	1,320	85	23	429
19	3,630	88	2,990	82	29	475
20	3,320	89	3,000	90	13	597

* B.T.P.S.
† Based on height and age.
‡ f = Breathing frequency.
§ V_T = Tidal volume.

TABLE 3

Gas Exchange Data in Obese Subjects

Case	P_{ACO_2}	P_{AO_2}	P_{aO_2}	$P_{AO_2}-P_{aO_2}$	$\frac{\dot{Q}va}{\dot{Q}t}\times 100$	$\frac{V_D}{V_T}\times 100$	Diffusing Capacity (Resting)	Hematocrit
	mm. Hg	mm. Hg	mm. Hg	mm. Hg			ml./min./mm. Hg	%
1	48	92	59	33	22–31	43		50
2	58	78	57	21	18–25	53		44
3	57	80*	46	34	40–50			61
4	37	110	73	37	15–20	53	11†	51
5	50	87	79	8	4–6	51	15†	39
6	46	89	75	14	7–10	42	46‡	40
7	45	92	68	24	14–19	46		41
8	35	104	78	26	10–14	21	17†	43
9	40	99	70	29	14–19	40	12†	39
10	56	81	71	10	6–9	55	26†	35
11	35	105	74	31	13–18	14	25†	52
12	41	98*	66	32	17–23			52
13	51	89	74	15	8–11	39		41
14	40	99	86	13	5–7	25	15‡	36
15	47	92*	65	27	17–23		21†	65
16	46	93	86	7	3–4	32	18§	51
17	59	81*	69	12	8–11			37
18	29	114	67	47	20–28	14		29
19	34	110	57	53	30–40	32		39
20	46	88	69	19	11–15	40		46

* Estimated for R = 0.8.
† For oxygen.
‡ For carbon monoxide, using the steady state, physiologic dead space method.
§ For carbon monoxide, using the breath holding method.

predicted according to height and age. The mean one-second forced expiratory volume was 82% of the vital capacity, suggesting no significant airway obstruction. The mean respiratory rate was 22 per minute, and the mean tidal volume was 465 ml.

II. Gas Exchange: 1. Alveolar and Arterial Gas Tensions. Gas exchange data are shown in table 3. Arterial (or alveolar) CO_2 tension (P_{ACO_2}) was normal (45 mm. Hg or less) in nine subjects, at the upper limit of normal (45 to 48 mm. Hg) in five, and elevated ($>$ 48 mm. Hg) in six. The mean value was 45 mm. Hg. Alveolar O_2 tension (P_{AO_2}, calculated from the alveolar air equation) was correspondingly normal in nine subjects, on the lower side of normal in five subjects, and low in the other six. The mean was 95 mm. Hg. Arterial oxygen tension, on the

TABLE 4

Effect of Body Position on Gas Exchange in Five Obese Subjects

Case	Condition	P_{aco_2}	P_{ao_2}	$\dot{Q}va/\dot{Q}t \times 100$	V_T†	f‡
11*	Supine	43	52	35–45		
	Sitting	34	91	9–13		
13	Supine	51	74	8–11	438	12.5
	Sitting	40	85	6–9	846	13.5
16	Supine	46	86	3–4		
	Sitting	51	69	12–18		
18	Supine	29	67	20–28	429	23
	Sitting	32	71	15–20	518	36
19	Supine	34	57	30–40	475	29
	Sitting	40	78	8–12	622	22

* Data on this subject represent a different study from that reported in table 3.
† V_T = Tidal volume.
‡ f = Breathing frequency.

other hand, was below normal in all subjects; the mean value was 70 mm. Hg. The alveolar-arterial P_{O_2} gradient varied from 7 to 53 mm. Hg, with a mean of 25 mm. Hg.

2. Distribution. The venous admixture, expressed as a percentage of the cardiac output ($\dot{Q}va/\dot{Q}t \times 100$), was increased above normal in all but two cases. The mean range was 13 to 18.§

The physiologic dead space, expressed as a percentage of the tidal volume ($V_D/V_T \times 100$), was measured in 16 subjects and found to be elevated (> 30) in 12. The mean value was 38.

3. Diffusion. Pulmonary diffusing capacity was slightly below average normal figures. However, if considered in relation to body weight or body surface area, the values were moderately reduced.

§ Since the mixed venous O_2 saturation was not measured in these subjects, a difference of 25 to 35% O_2 saturation was assumed between pulmonary "end-capillary" and mixed venous blood.

III. Hematocrit: The hematocrit was increased in three of six male subjects with a mean of 50% and was increased in four of fourteen female subjects with a mean of 42%.

IV. Effect of Supine vs. Sitting Position: Studies were performed in both positions in five cases (table 4). Although the change in arterial CO_2 tension was not consistent, in four cases venous admixture was lower and arterial O_2 tension was higher in the sitting position. Comparison of breathing depth and frequency was available in three of these cases, and showed a larger tidal volume in the sitting compared to the supine position.

V. Effect of Deep Breathing: In addition to the studies performed in the sitting position, where breathing was deeper than in the recumbent position, one subject (case 18) was asked to take three deep breaths and then to resume quiet breathing. Arterial blood was drawn during the minute following the three deep breaths. Although the arterial CO_2 tension had not dropped, the arterial O_2 tension increased from 67 to 72 mm. Hg.

Comments

All 20 subjects showed some degree of reduction in arterial oxygen tension. Since hypoventilation (CO_2 retention) was present in only eight of the subjects, it is evident that the mechanism of arterial hypoxia was not always on the basis of hypoventilation. Furthermore, even in the subjects who exhibited CO_2 retention, the degree of arterial deoxygenation was, in all but one (case 5), greater than could be accounted for simply by the elevated arterial CO_2 tension. The pulmonary diffusing capacity was not reduced sufficiently to account for the abnormally low arterial oxygen tension present in the resting condition. Since the venous admixture and physiologic dead space ratios were abnormally elevated, one is forced to the conclusion that the basic disorder in gas exchange in cases of obesity is one of distribution—that is to say, a disturbance in ventilation-perfusion relationships [23] (figure 1).

The question now is: Why should obesity lead to a disturbed ventilation-perfusion relationship? The answer may lie in the way most obese subjects breathe, namely, a rapid, shallow and often irregular breathing, which takes place at a smaller lung volume, i.e., in a more nearly expiratory position. Experiments in dogs by Mead and Collier,[24] and studies on convalescent poliomyelitic patients by Ferris and Pollard [25] suggest that prolonged shallow breathing was complicated by regional atelectasis due to small airway closure. The effect was reversed by a series of deep breaths. Similarly, McIlroy et al.[26] and others [27, 28] produced increased physiologic shunts (venous admixture) in normal subjects by strapping the chest, a procedure which imposed a load on the chest bellows not unlike that of obesity. It is possible, therefore, that the shallow breathing of the obese at a small lung volume causes small airway closure and regional atelectasis leading to increased venous admixture. It is also possible that shallow and irregular breathing

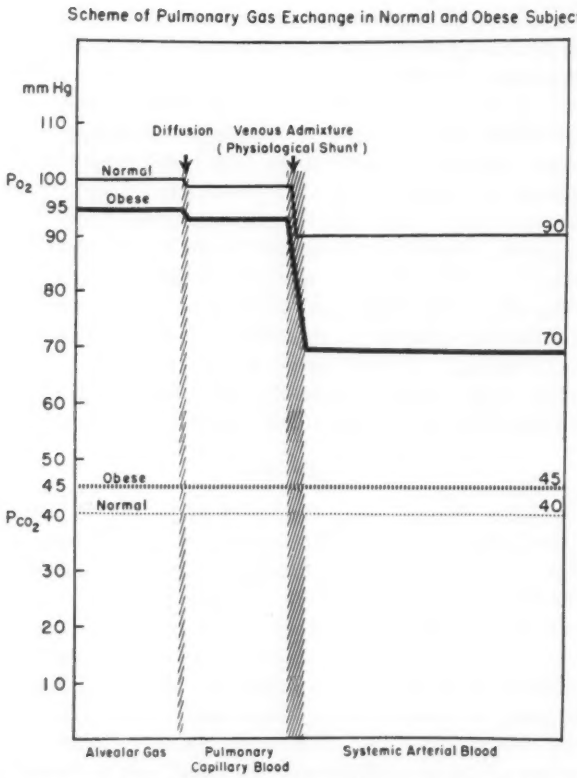

FIG. 1. Plot of O_2 and CO_2 tension in the alveolar gas, the pulmonary capillary blood and the systemic arterial blood in normal and in obese subjects.

In the normal, the CO_2 tension in the alveoli averages 40 mm. Hg, and the O_2 tension averages 100 mm. Hg. Whereas arterial CO_2 tension is practically the same as alveolar CO_2 tension, arterial O_2 tension is about 10 mm. Hg below alveolar O_2 tension. This O_2 tension gradient is due mainly to admixture of venous blood from poorly ventilated alveoli and from anatomic channels. This is referred to as venous admixture, or physiologic shunt. A very small fraction of the gradient is due to resistance offered to diffusion of O_2.

In the 20 obese subjects studied, the alveolar (or arterial) CO_2 tension was 45 mm. Hg. The alveolar O_2 tension was correspondingly reduced but was not much below normal (95 instead of 100 mm. Hg). The arterial O_2 tension, however, was significantly reduced (to 70 mm. Hg), and the alveolar-arterial O_2 pressure gradient was increased from a normal of 10 to 25 mm. Hg. Although the diffusion component of the gradient was slightly increased, the large gradient was due chiefly to a large venous admixture component, which must be due to uneven alveolar ventilation in relation to perfusion.

deprives the pulmonary capillary circulation of the important pumping action by which normal respiratory movement promotes uniformity of capillary perfusion. Uneven perfusion of alveoli will, of course, result in a disturbed ventilation-perfusion ratio, with an increase in physiologic dead space and in physiologic shunt.

The studies in which patients were examined in the supine and sitting

positions lend further support to this theory. Although the number of subjects studied is small, there appears to be less abnormality of gas exchange in patients while in the sitting position. The larger tidal volume, and the lower position of the diaphragm with resultant larger lung volume in the sitting position, are probably responsible for this effect of position.

A schema of the basic physiologic mechanisms leading to abnormal gas exchange in obesity is shown in figure 2.

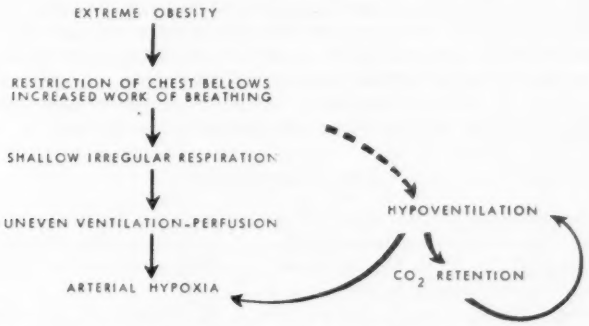

FIG. 2. Possible physiologic mechanisms leading to abnormal gas exchange in obesity.

SUMMARY

1. Pulmonary gas exchange was studied in 20 obese subjects.

2. Some lowering of arterial oxygen tension was present in all subjects, whereas evidence of hypoventilation (arterial CO_2 tension above 48 mm. Hg) was found in only eight.

3. The suggestion has been made that a disturbed alveolar ventilation-perfusion relationship is a basic abnormality of gas exchange in the obese.

4. Shallow and irregular breathing in a more nearly expiratory position is a possible cause of this disturbed relationship.

5. It is possible that CO_2 retention is a relatively late development in the evolution of respiratory dysfunction due to obesity.

ACKNOWLEDGMENT

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SUMMARIO IN INTERLINGUA

Pro determinar le incidentia e le natura de insufficientia pulmonar in obesitate, 20 obese subjectos sin antecedentes de morbo cardiac o pulmonar esseva studiate. Un certe grado de hypoxia arterial esseva presente in omne le subjectos. Hypoventilation (i.e. alte valores de P_{CO_2} arterial) esseva presente in solmente octo del subjectos. Le gradiente alveolo-arterial pro P_{CO_2} in stato de reposo e durante le respiration de aere normal esseva augmentate. Viste que le capacitate diffusori del pulmones esseva trovate intra le limites normal o levemente infra illos, il seque que le augmentate gradiente esseva quasi in toto le resultato de un augmento del admixtion

venose. Etiam le spatio morte physiologic esseva augmentate. Iste resultatos signala non-uniformitate del distribution del ventilation alveolar in relation al perfusion. Es opinate que le anormalitate del proportion de ventilation a perfusion es relationate a duo factores. Le respiration irregular, rapide, e pauco profunde que es characteristic de subjectos obese resulta possibilemente in non-uniformitate del perfusion alveolar per disrangiar le normal action "pumpante" del movimentos respiratori le quales—normalmente—promove le uniformitate del perfusion. In plus, iste typo de respiration pone le pulmon in un position plus tosto expiratori, i.e. un position in que il existe un plus grande probabilitate que micre vias aeree es claudite, con le resultato de atelectasis regional e non-uniforme ventilation-perfusion alveolar. Es concludite que extreme obesitate pote disturbar le excambio pulmonar de gas sin causar hypoventilation. Anormal proportiones de ventilation a perfusion es un constatation commun, resultante probabilemente del respiration irregular e superficial e del respiration in position expiratori. Hypoventilation es apparentemente un disveloppamento tardive in le evolution de dysfunction respiratori in consequentia de obesitate.

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VIRAL AND RICKETTSIAL CAUSES OF CARDIAC DISEASE, INCLUDING THE COXSACKIE VIRUS ETIOLOGY OF PERICARDITIS AND MYOCARDITIS * †

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Introduction

Pyogenic pericarditis is well known and, in contrast to the benign, nonspecific types, is frequently fatal. Rheumatic carditis is common and readily recognized, as a rule. Myocarditis of viral, rickettsial, granulomatous or nonspecific etiology is less frequent clinically, and may be overlooked. Improved laboratory technics within the last decade have provided more accurate identification of virus diseases, and thereby made possible the detection of specific types of pericarditis and myocarditis.

Myocarditis

Jean Corvisart had sufficient vision to describe accurately the natural history of myocarditis when, in 1812, he wrote concerning acute carditis: "Hence this inflammation almost always terminates fatally; but the death which it usually occasions may happen instantly or somewhat slowly. Thus carditis has been known to become fatal in a very few days; while in other instances, when the disease has attained to its highest degree, the most alarming symptoms partially disappear, and a sort of convalescence is established; sometimes even the patient is restored to apparent health; he then flatters himself with a near perfect cure; but the most intelligent physician perceives only a transformation, or degeneration of the disease into another affection; but not less severe, as a chronic organic disease is then established, mortal in all cases." [1]

When patients develop apparently causeless heart failure, the diagnosis of myocarditis is made occasionally, although hypertension or painless coronary disease is diagnosed frequently. The clinical features of cardiomyopathy, particularly rheumatic carditis, are well known and are discernible readily at the bedside. Precordial discomfort or dyspnea on effort

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may be the initial complaint. Palpitation is troublesome, arrhythmias are frequent, and cardiomegaly with gallop rhythm, elevation of jugular venous pressure, and edema throughout the body is noted in the advanced case. The symptoms may progress quietly, and yet sudden death is not uncommon in patients with acute and chronic myocarditis. Several reviews of the subject [2, 3, 4] describe the clinical features and specific causes of the common myocardial diseases. They cover the subject comprehensively up to the time of their publication.

The infective forms of myocarditis are almost as numerous as the microbial agents. Myocarditis associated with the common infections occurs either simultaneously or as a sequel to the acute illness. Types not described specifically include postdiphtheritic myocarditis,[5, 6, 7] those associated with typhoid and paratyphoid fever,[2] bronchopneumonia, lobar pneumonia,[2, 4] bronchiectasis,[2] pertussis,[2] pharyngitis, tonsillitis,[8] meningococcic and streptococcic meningitis,[2, 4] acute and subacute endocarditis,[2, 4] leptospirosis [4, 9] and tuberculosis of the miliary and diffuse types.[2, 4, 10] The viral diseases are represented by measles,[11, 12] mumps,[4] poliomyelitis,[4, 13] varicella,[14] variola,[15] infectious hepatitis,[16] yellow fever,[17] psittacosis,[18] infectious mononucleosis,[19] epidemic hemorrhagic fever [20] and encephalomyocarditis.[21, 22, 23] Isolated, or Fiedler's, myocarditis of unknown cause is an established entity.[24] Instances of myocarditis associated with syphilis,[4] infectious granulomata,[4, 25] mycoses,[4] protozoa,[4] and helminthic diseases [4] are not common.

We have studied patients with myocarditis caused by viral or rickettsial agents in whom the clinical manifestations of myocardial involvement were clearly evident. Several illustrative case presentations follow:

Case Reports

Coxsackie Disease

*Case 1 (Neonatal myocarditis).** This white male child appeared to be normal at the time of birth. Two days prior to the advent of labor his mother had experienced a brief episode of grippe but was asymptomatic at delivery. Three days following delivery she developed an illness associated with fever, malaise and leukopenia which persisted for 72 hours. On the fourth postnatal day, the baby developed fever, irritability and marked tachycardia. He remained febrile for about four days, during which time no bacterial cause for the illness was found. Tachycardia decreased during this period, and the baby remained afebrile. There was gradual improvement until the fourteenth postnatal day, when tachycardia suddenly recurred and the child died.

Agents pathogenic for suckling mice were isolated from the baby's stool on the fourth day of disease, and from the myocardium on the day of death, the eleventh day of illness. Both agents, also recovered in the FL line of human amnion, were identified as Coxsackie B, type 2 viruses. Serum obtained from the child during the illness failed to show Coxsackie B antibodies. However, type 2 neutralizing antibody was demonstrable in the mother's serum by the eighteenth day of disease.

* The case record, including laboratory and pathologic findings, will be reported by Dr. Anthony Perlman elsewhere.

One additional case of fatal neonatal myocarditis caused by Coxsackie virus, group B, type 2 was studied recently. Death of the infant occurred on the ninth day of life. On histologic examination there was extensive focal myocarditis, consisting of dense mononuclear infiltrates and necrosis of myocardial fibers (see figure 1). A virus pathogenic for suckling mice was isolated from the infant's myocardium, and serum-neutralizing antibody to that virus was demonstrated in the mother's serum in the titer of 320.

Case 2 (*Adult myocarditis*). A 26 year old man developed chills, fever and headache three days prior to the development of anterior chest pain which was exaggerated by deep inspiration. The pain radiated to the left shoulder and left upper abdominal quadrant. The past history was negative. After hospitalization on the third day the temperature was 103° F.; pulse, 120; respiratory rate, 20. The temperature fluctuated from 100 to 104° F. for one week. The pertinent physical findings included tachycardia (range, 100 to 120), moderate cardiomegaly and pulmonary râles. The blood pressure was 110/70 mm. of Hg. Neither a gallop rhythm nor a pericardial friction rub was detected. Signs regarded as unmistakable for the

TABLE 1

Results of Coxsackie Virus Studies of Case 1 and Mother

Specimen	Day of Disease	Virus Isolation		Serum Neutralization					Titer
		Tissue Culture	Suckling Mouse	B1	B2	B3	B4	B5	Patient's Virus
Infant									
Stool	4	B2	B2						
Myocardium	11	B2	B2						
Serum	2			<5	<5	<5	<5	<5	<5
Serum	11			10	<5	<5	<5	<5	<5
Mother									
Serum	4			10	160	<5	<5	<5	80
Serum	18			40	650	<5	<5	<5	320

presence of myocarditis were: cardiomegaly, as demonstrated by physical and roentgen findings, tachycardia with slight pulmonary congestion, and electrocardiographic abnormalities. Digitalis was not given. X-ray examination of the lungs was repeatedly negative. Definite cardiomegaly was noted on the sixth febrile day, and was confirmed subsequently by roentgenogram (figure 2). Cardiac size had diminished appreciably by the fourteenth day of disease. Electrocardiographic findings on the eighth febrile day were indicative of myocardial involvement, i.e., PR interval, 0.16 sec.; QRS, 0.11 sec.; terminal slurring of S waves in Leads 2, 3, aVF, V5, V6, rs, rs′, V1 and V2. T waves were inverted in V1 and V2, and notched in V3. These findings suggested incomplete right bundle branch block. On the eleventh day the atrioventricular conduction time had increased to 0.20 sec. There was slight elevation of the ST segments in Leads 1, 2, 3, aVF, V2, V3, V4, V5 and V6. After 14 day of illness the electrocardiogram had reverted to normal, with a PR interval of 0.18 sec. and QRS of 0.09 sec. QRS complexes, ST segments and T waves normal.

The patient improved rapidly after defervescence, which occurred in one week. There were no detectable abnormalities at the time of hospital discharge on the sixteenth day of disease. The sedimentation rate was 24 and 19 mm. on two occasions, and there were no significant abnormalities of the urine or blood (leukocyte

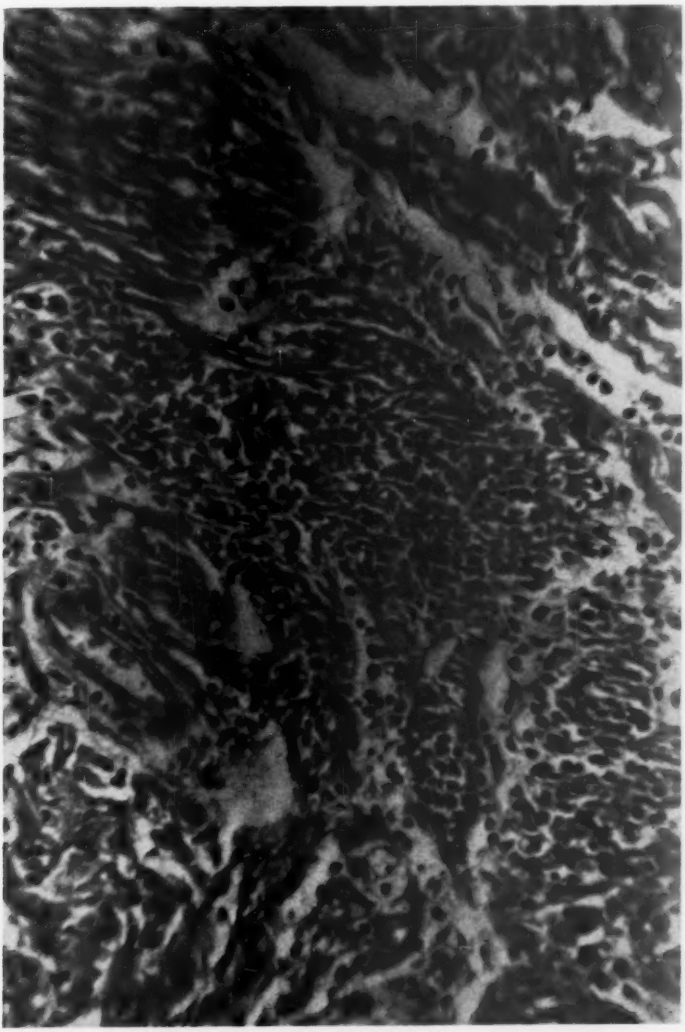

FIG. 1. *Neonatal myocarditis.* (Coxsackie Virus, Group B, Type 2.) Myocardium of infant dying of Coxsackie virus myocarditis on the ninth day of life. Note area of focal myocarditis, dense mononuclear infiltrate, vascular congestion, edema and myocardial necrosis.

count, 7,250 to 7,700 per cubic millimeter; hemoglobin, 12.9 gm., 85%; blood culture, sterile; urinalyses, normal; serologic test for syphilis, negative).

Agents pathogenic for suckling mice or tissue cell lines were not isolated from a stool specimen collected in the second week of illness. A serum specimen taken on the tenth day of disease showed a serum neutralization titer of 160 for Coxsackie

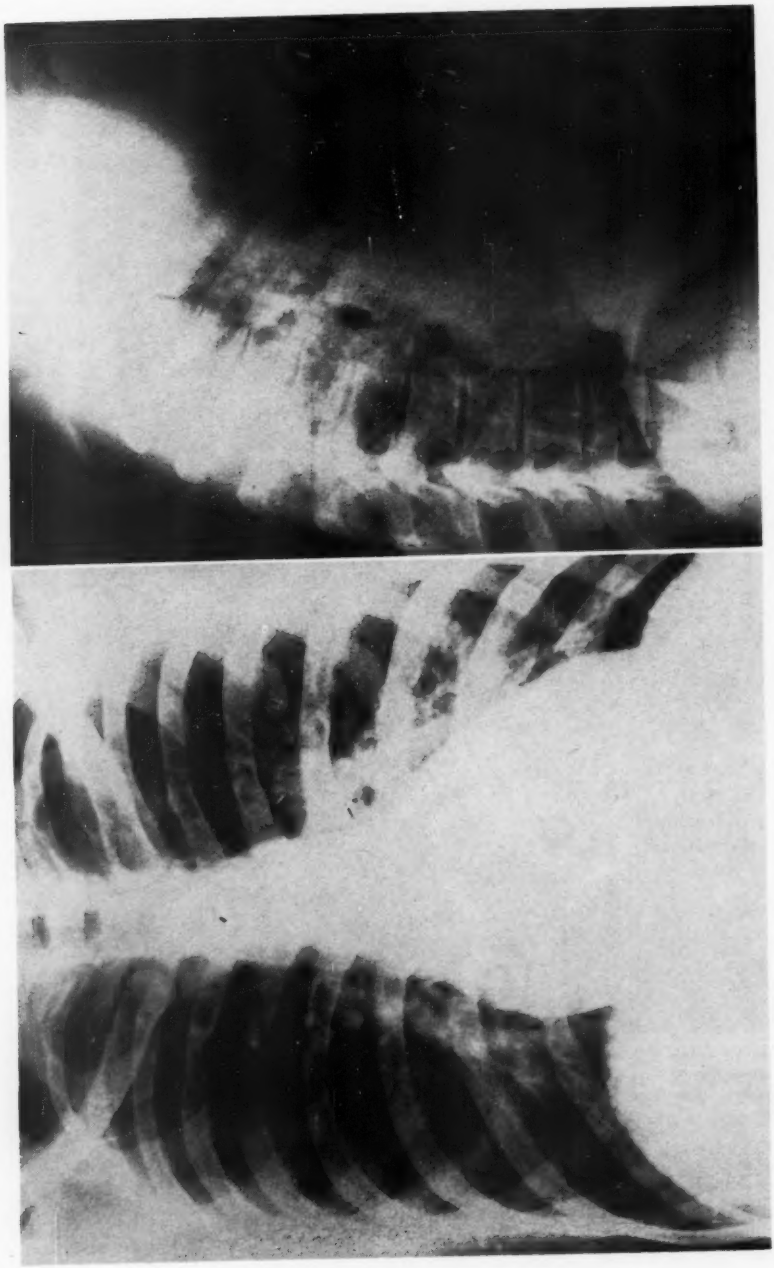

FIG. 2A. *Case 2. Adult myocarditis, Coxsackie type.* Roentgenogram of a 26 year old man taken on the fifth day of illness, showing cardiomegaly and slight pulmonary congestion. Note enlargement of left ventricle on lateral view.

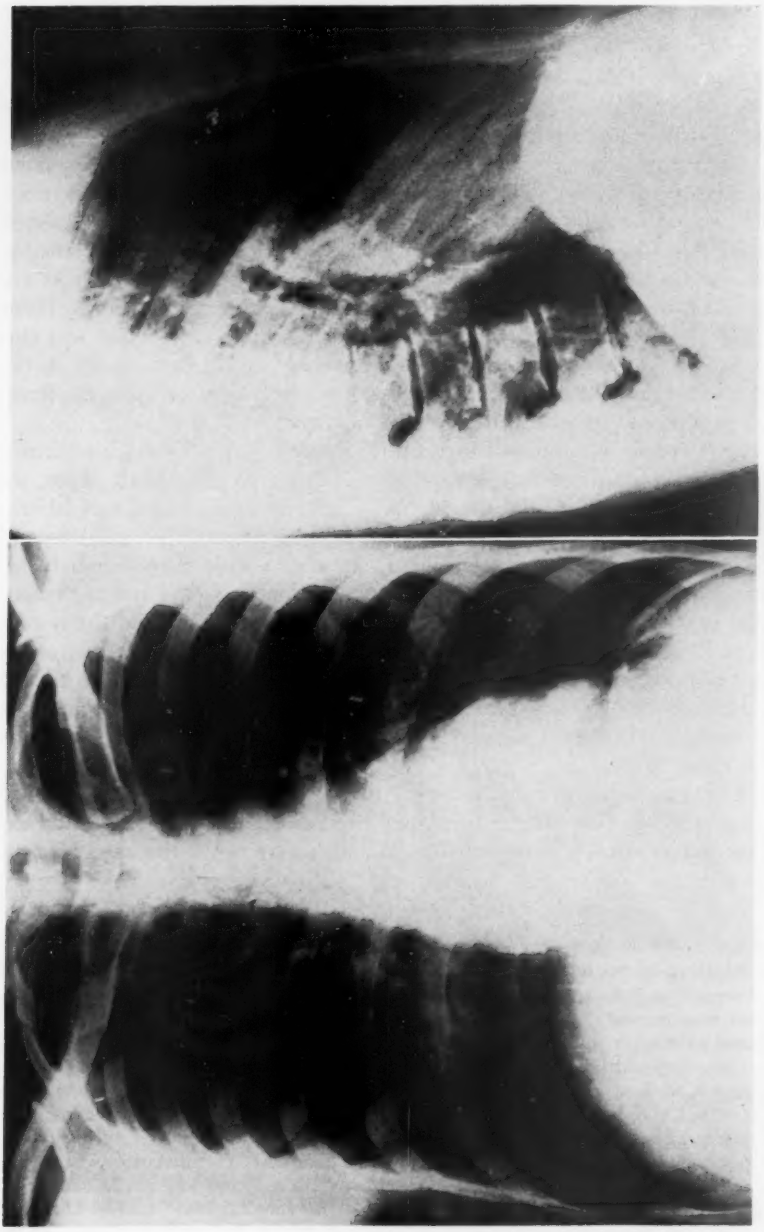

FIG. 2B. *Case 2.* Convalescent film taken on the sixteenth day of illness, showing reduction of cardiac size to normal.

virus, group B, type 2. A subsequent specimen taken on the twenty-fifth day of disease was positive in the titer of 1,280.

Comment: The Coxsackie viruses, particularly group B, have been specifically incriminated as infective causes of acute myocarditis. Javette et al.[26] demonstrated that the myocardium of newborn babies may bear the direct brunt of attack by this virus. Coxsackie virus has been isolated from the myocardium and feces, and characteristic morphologic alterations of diffuse and focal myocarditis, with necrosis in humans and in inoculated animals, have been demonstrated.[26, 27, 28, 29] Cocksackie virus has been isolated from the feces of mothers bearing these children.[29] Two examples are reported of myocarditis caused by Coxsackie virus types 4 and 2 in an infant and a child, aged seven weeks and five years, respectively.[30] Virus was isolated from the infant's myocardium, and the diagnosis of myocarditis in the child is based on typical clinical findings, the recovery of virus from the feces, and a significant rise in titer to the specific virus.

The detection in adults of myocarditis caused by the Coxsackie viruses has lagged behind the pediatric experience. After preparing this paper, we noted the report of Null and Castle,[31] who described the clinical and laboratory findings of two adult patients, aged 24 and 35, with pericarditis and myocarditis, in whom Coxsackie virus appears to have been definitely incriminated. In one patient a serum neutralization titer of 128 was demonstrated in specimens of serum examined on the twenty-first and thirty-first days of illness. Laboratory confirmation of the clinical diagnosis was on firmer evidence in the second case, since Coxsackie virus group B, type 5 was isolated from pharyngeal washings and feces. Serum examined on the fourth day of illness showed a neutralizing titer of 128 for Coxsackie virus, group B, type 5.

The examples of neonatal and adult myocarditis caused by the Coxsackie viruses here reported add to the rapidly increasing number of specific examples, and confirm that myocarditis in adults may result from infection by these agents.

Influenza

Case 1. A 20 year old housewife was hospitalized with cyanosis, delirium and physical signs of bilateral basilar pneumonitis on the seventh day of a respiratory infection. The pulse rate was 145; blood pressure, 100/50 mm. of Hg. Gallop rhythm was present. A chest roentgenogram revealed bilateral patchy, somewhat confluent pulmonary infiltration. The patient was desperately ill for several days with tachypnea, tachycardia, cyanosis and gallop rhythm. By the tenth day the electrocardiogram showed delayed conduction and ST segment and T wave changes in the standard and lateral precordial leads, indicative of nonlocalized myocardial involvement. The blood leukocyte count was 10,500 per cubic millimeter. *Hemophilus influenzae* was isolated from the sputum. The diagnosis of influenza, Asian type, was confirmed by a rise in titer for HI antibody from 1:160 to 1:5120 during the illness. Satisfactory recovery ensued despite a very stormy course. Oxygen, penicillin and chloramphenicol were administered. The cardiovascular and electrocardiographic abnormalities were normal within two months from the onset.

FIG. 3. *Case 2. Influenza myocarditis.* Myocardium of a 17 year old gravid woman who died on the fourth day of illness. Note capillary engorgement and interstitial mononuclear cell infiltrate.

Case 2. A 17 year old gravid woman developed pharyngitis, cough and malaise at the time of the epidemic of influenza in 1957. After three days' remission, she became ill suddenly, with marked dyspnea, fever, toxemia and extreme weakness. Death occurred on the same day. Microscopic examination of the myocardium showed large numbers of mononuclear cells infiltrating the interstices, and capillary engorgement. No Aschoff's nodules were observed (figure 3). The lungs showed bilateral nonsuppurative pneumonitis, edema and hyaline membrane formation, consistent with a diagnosis of influenza.

Comment: Influenza may cause acute inflammation of the myocardium.[32] Mackenzie reported myocardial damage in autopsy material, and assumed that "influenza may be the beginning of a myocarditis which leads ultimately to heart failure."[33] This author concluded, however, that patients who already had heart failure passed through an attack of influenza "scatheless." Lewis opposed this view, and reported the deaths of two patients on a cardiac ward who contracted influenza.[34] Hamburger[35] held that some patients do not recover from influenza completely, and develop postinfluenzal myocardial insufficiency with conduction abnormalities. Conceivably, some of these patients had rheumatic heart disease.

Finland et al.[36] correlated in two patients the clinical findings, histologic evidence of severe focal myocarditis, and virus isolation (identified as PR 8, Group A) from the lungs. One patient died of heart failure, and the other died of extensive bronchopneumonia. The recent pandemic of Asian influenza in 1957 was mild, although fatalities were reported. Clinical evidence of myocarditis was reportedly uncommon, yet of 20 or more severely ill patients observed by us, one developed clinical evidence of transient myocarditis, and another who succumbed showed an interstitial inflammatory reaction.[37] One instance of myocarditis was reported by Giles and Shuttleworth in 46 patients who died of influenza virus infection, Asian type.[38] Oseasohn and his associates[39] reported varying degrees of acute inflammatory focal, interstitial and diffuse myocarditis in 10 patients with Asian influenza. In one patient, virus identified as the Asian type was isolated from the myocardium which showed fibrinoid degeneration of arteriolar walls and focal fibrin thrombi. On the basis of clinical and morphologic data, the presence of myocardial injury by influenza is not uncommon.

Poliomyelitis

Case 1. A Negro child, aged 19 months, was hospitalized at the Baltimore City Hospital on the fourth day of an illness characterized by vomiting and tachycardia. Except for varicella and measles at three months, the child had been healthy prior to the present illness. Signs of cardiomegaly, pulmonary congestion, and hepatomegaly were found on admission. The heart rate was 160; blood pressure, 105/20 mm. of Hg; respiratory rate, 32. A chest roentgenogram confirmed the presence of cardiomegaly, and showed accentuated vascular markings and minimal pleural fluid. The heart was definitely smaller in three weeks, and normal in size approximately six weeks from onset of illness. Serial electrocardiographic studies showed conduction defects and T wave changes compatible with nonspecific myocardial changes. ST segment abnormalities and signs of left ventricular enlargement occurred during the active stages. Within three weeks from the onset of illness, the electrocardiographic findings were normal. During hospitalization the temperature ranged between 99.6 and 100.2° F.

Except for moderate anemia (hemoglobin, 7.5 gm.) and leukocytosis (10,750 to 12,250 per cubic millimeter), there were no significant clinical pathologic abnormalities. The antistreptolysin titer did not exceed 125 Todd units. The tuberculin skin test was negative. Polio vaccine had not been given. Table 2 presents the results of the serologic and virus studies. It may be seen that polio virus Type I was isolated

from the feces, and a fivefold rise in serum neutralizing antibody to this virus was demonstrated. Antibody studies for Coxsackie virus disease were negative.

Comment: The cardiovascular abnormalities associated with poliomyelitis include tachycardia, pulmonary congestion, occasionally hypertension, morphologic alterations of the myocardium, electrocardiographic changes and shock. The most common lesion in the cardiac muscle, which has been reported in from 40 to 90% of patients dying from poliomyelitis, consists of focal interstitial collections of lymphocytes.[13] A less common type of myocarditis in poliomyelitis consists of necrosis of cardiac muscle fibers and

TABLE 2

Results of Poliomyelitis Virus Studies in Case 1

Source of Specimen	Day of Disease	Virus Isolation		
		Polio	Coxsackie	
Nasopharyngeal washings	71	0	0	
Stool	12	Type I	0	
		Serum Neutralization Titer		
		Type I	Type II	Type III
Serum	4	<5	<5	<5
	90	80	<5	<5

a neutrophilic infiltrate. Poliomyelitis virus has been isolated from the myocardium of fatal cases.

MYOCARDITIS IN THE RICKETTSIAL DISEASES

The rickettsioses are characterized by distinctive pathologic changes in the small vessels, particularly the endothelial cells. Fall in blood pressure or circulatory collapse is an outstanding feature of the rickettsial diseases, and myocardial involvement may play an additional role in some cases. An illustrative example is shown by the following patient with Rocky Mountain spotted fever.

ROCKY MOUNTAIN SPOTTED FEVER

Case 1. A 70 year old farmer was hospitalized on the seventh day of an illness characterized by fever, vertigo, weakness, headache and malaise. A tick was imbedded in the skin of the right axilla. The patient was toxic and partially incoherent. Conjunctival injection was present. A faint pink macular rash was noted over the abdomen and extremities. Terramycin treatment was instituted. On the following day (eighth day of illness), the patient became unresponsive, the blood pressure fell from 120/80 to 90/60 mm. of Hg, and signs of vascular collapse developed, i.e., cold extremities, cyanosis of the lips and gums, and a totally irregular pulse with a rate of 120. Fruitless attempts at corrective measures included the administration of plasma

infusions and neosynephrine. The rash became diffuse and ecchymotic, covering most of the body. Death occurred on the second hospital day. The electrocardiogram revealed signs of myocardial injury, i.e., low voltage, slurring and notching of the QRS complexes, and auricular fibrillation.

The diagnosis of Rocky Mountain spotted fever was confirmed by isolation of *Rickettsia rickettsii* from the blood. Agglutinins to Proteus OX 19 and rickettsial complement-fixing antibodies were not demonstrable at the time of death. The blood leukocyte count was 3,400 per cubic millimeter.

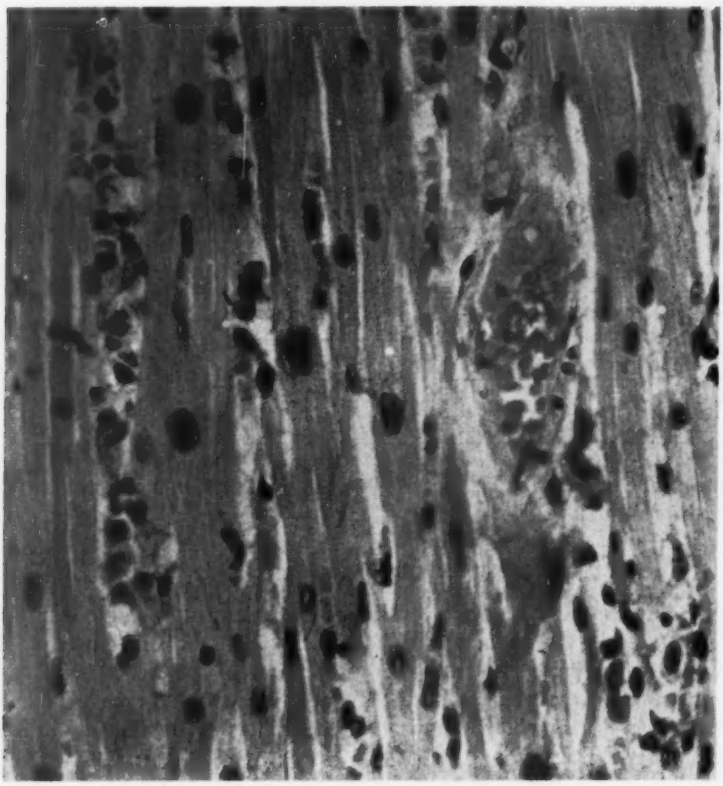

FIG. 4. ***Case 1. Myocarditis, Rocky Mountain spotted fever.*** Myocardium of a 70 year old patient dying on the ninth day of disease. Note mononuclear and plasma cell infiltration, with moderate interstitial edema and capillary congestion.

The heart weighed 350 gm. The epicardium was separated from the myocardium by connective tissue infiltrated with mononuclear cells. There were moderate interstitial edema and mononuclear cell infiltration. Capillary dilatation was noted, and in some areas the myocardial fibers were pale.

Comment: On the basis of study of the individual lesions, it is difficult to distinguish Rocky Mountain spotted fever from epidemic typhus or

tsutsugamushi disease. The distinctive alteration of the rickettsioses is damage to small blood vessels.[40, 41, 42] Perivascular accumulation of cells and cellular infiltration of organs may be diffuse. Acute interstitial myocarditis with diffuse infiltration by mononuclear cells occurs in each of the rickettsial diseases (scrub typhus, epidemic typhus and Rocky Mountain spotted fever, in descending order of frequency).

In severe scrub typhus,[43] epidemic typhus[44, 45, 46] and Rocky Mountain spotted fever,[47] minor cardiac signs occur in the first week of illness. Later in the second week, heart sounds are often poor in quality, the first heart sound is soft, and apical or basal murmurs occur. Cardiomegaly is slight. The pulse may be rapid, thready and irregular, with periods of ectopic beats or atrial fibrillation. Gallop rhythm occurs but is unusual. During this stage there is persistent hypotension. Venous pressures are usually normal or low. There is no distinctive electrocardiographic pattern attributable to either of the three rickettsial diseases. In scrub typhus, electrocardiographic changes consist of flattening of T waves, ST elevations, bundle branch block, atrial fibrillation and complete heart block. In Rocky Mountain spotted fever, serial electrocardiograms reveal T wave changes and, rarely, prolongation of PR intervals.[46] Similar alterations, including deformity of the ST segment, are sometimes observed in patients with epidemic typhus. Most of these abnormalities are transient.

Blake[43] regarded the circulatory failure seen in severe and fatal cases of scrub typhus as a phenomenon of peripheral origin, rather than as due to heart failure per se. This position was taken in spite of the variable degrees of myocarditis noted in fatal cases. A clear correlation between electrocardiographic alterations and mortality is not present. As in Rocky Mountain spotted fever and epidemic typhus, permanent cardiac damage is rare in scrub typhus. Wolbach[40] concluded that in none is there much evidence of degeneration of heart muscle, and questioned the relationship of the "myocarditis" to cardiac function.

Our opinion is that the fall in blood pressures and circulatory collapse, which are outstanding features of the rickettsial diseases, result primarily from changes in the peripheral circulation.[44] Nevertheless, there are evidences of direct myocardial involvement, as demonstrated by the clinical and morphologic findings of the case presented. The cardiac manifestations are transient, and there is little evidence of perpetuating cardiac dysfunction in recovered patients. The contribution of the myocardial abnormalities during the acute illness may be significant.

Discussion of Myocarditis

The myocardium may be damaged by different mechanisms. Direct enzymatic injury of cardiac muscle fibers, with fragmentation and necrosis, occurs in pyogenic myocarditis. The rickettsial lesion is primarily a vasculitis. Rickettsiae damage endothelial cells directly, and their toxins promote

capillary leakage. Viruses multiply within tissue cells and occasionally produce extensive vascular lesions in the myocardium, including interstitial infiltration and muscle fiber fragmentation. Diphtheritic and other bacterial toxins are protoplasmic poisons which alter cellular respiration.

Experimentally, the endotoxins of gram-negative bacteria produce fibrinoid in the walls of coronary vessels, and myocardial myofiber destruc-

FIG. 5. *Experimental myocarditis in rat.* Myocardium showing area of focal inflammation and interstitial cellular reaction.

tion in the right heart and septum chiefly.[48] These changes resemble the overwhelming intoxication by epinephrine, or the syndrome of traumatic shock. In rabbits and rats, small doses of bacterial endotoxin heighten the the vascular response to epinephrine, whereas large doses lead to a refractoriness to adrenalin. Conversely, Greisman and Wisseman[49] showed that

the toxins of *Rickettsia mooseri* fail to alter the reactivity of the arterioles of the rat to adrenalin. Studies of this nature may help to clarify certain underlying mechanisms in the pathogenesis of myocarditis. Christian suggested that the frequent cases of chronic nonvalvular disease may have their inception in acute lesions of the myocardium which appeared during the course of some acute infectious disease.[50]

Several years ago we prepared a cardiotoxic serum of low potency by inoculating rabbits repeatedly with rat heart tissue. The consequent rabbit serum contained anti-rat heart antibody and, on inoculation into normal rats, provoked a mild interstitial cellular myocardial reaction. The technics employed resembled those of Smadel, who prepared a nephrotoxic serum.[51] When rats so prepared developed superimposed bacterial infections, a diffuse inflammatory myocarditis ensued. The relationship of the antigen-antibody type of myocarditis to the subsequent pyogenic cardiac infection is unclear and merits clarification.

Endotoxins, catecholamines and abnormal antibodies could incite further damage in a properly prepared host. These mechanisms would presumably be the exception rather than the rule. Many microbial diseases are characterized by toxemia and disturbed metabolic equilibria. Moreover, a virus, a microbe or its toxin may directly injure or sensitize a myocardial fiber or its membrane, a cardiac vessel or its endothelium. Usually, myocardial injury in infections is self-limiting and with recovery in such disorders as diphtheria, typhoid fever, rickettsial diseases, mumps and others, there are no significant detectable residua. Such may not necessarily be the case, and conceivably a vascular or tissue cell, once injured or sensitized to one type of antigen, may react unfavorably to that antigen or to a heterologous antigen following further exposure.

It is our belief that mild focal and interstitial myocarditis accompanying many infectious processes may be significant. Although the clinical manifestations of myocarditis are transient and apparently reversible, conceivably the tissue alteration may prepare the site for progressive or *de novo* developments later.

Confirmation of such a hypothesis necessitates careful study of the initial illness which would relate the clinical manifestations to a specific infectious cause. Subsequent appraisal would require painstaking, long-term observations, with special emphasis upon detection of overt or subtle clinical, biochemical, microbiologic and immunologic abnormalities during the course of all infections and throughout the ensuing years. The final clues would be derived from the morphologic alterations of the myocardium following death. A study of this type requires the continuous collaboration and patience of various dedicated investigative groups.

Our current studies serve mainly to confirm the causative role of newly characterized pathogens in myocarditis, and to call attention to the etiologic significance of recognized microbial agents.

Pericarditis

Recognition of benign pericarditis is not usually difficult. Sudden onset of precordial or epigastric pain, accentuated by respiration, suggests the presence of a friction rub, which is heard characteristically in the early stages. Numerous reports emphasize the characteristic findings and features, such as cardiomegaly,[52, 53] associated lung and pleural involvement,[52, 53, 54] the occasional presence of serosanguineous pericardial effusions[55, 56] and electrocardiographic abnormalities.[52, 53, 57] One report of a fatal case of nonspecific pericarditis emphasizes that anticoagulant therapy may be harmful.[58]

Christian had the foresight to write in 1951, in his last published paper concerning pericarditis: "As studies so far made of the pericardial fluid, unfortunately not very numerous, have failed to show a bacterial cause, there is good probability that some virus is causative, and this is suggested by its not infrequent sequence to the common cold and respiratory tract infections which so often now are regarded as forms of virus disease."[55]

The association of acute benign pericarditis and certain specific and nonspecific virus diseases has been reported. Lymphogranuloma venereum has been accompanied rarely by this complication.[59] Approximately 12 instances of pericarditis complicating infectious mononucleosis have been reported.[60] Fibrinous pericarditis with effusion has followed infections of the respiratory tract[61] and the syndrome of primary atypical pneumonia.[62] Conceivably, Coxsackie viruses may have been responsible for certain of these illnesses.

We recently observed patients with nonsuppurative pericarditis in whom it appears that the Coxsackie viruses may reasonably be incriminated.

Coxsackie Pericarditis

Case 1. A 51 year old physician noted headache and malaise approximately 10 hours before being awakened by a moderately sharp retrosternal pain, aggravated by breathing, with radiation to the neck and ears. The patient did not regard himself as being ill enough to suggest an attack of myocardial infarction. There was no nausea, vomiting, or sweating. His physician detected no abnormal signs at the time of onset other than fever. The retrosternal pain persisted and radiated cephalad to the neck, pharynx, teeth and ears. The temperature ranged from 101 to 103° F., and for several days deep breathing aggravated the pain. A pericardial friction rub was heard on the sixth febrile day, when approximately 100 ml. of serous fluid were aspirated from the left pleural space. An electrocardiogram showed nonspecific changes indicative of myocardial damage or pericarditis. The patient improved steadily until about five weeks from defervescence, when the fever, precordial pain and pericardial rub recurred. The second episode was mild, and the patient was fully recovered two months from the initial onset of illness.

Several chest films revealed left hydrothorax, which subsided gradually. Cardiomegaly was not noted. Serial electrocardiograms revealed ST segment, T wave changes and low voltage, indicative of pericarditis rather than of coronary artery disease and myocardial infarction. The electrocardiogram was essentially normal four months after onset.

The tuberculin skin test was negative on two occasions. The sedimentation rate, C-reactive protein, and blood leukocyte count were elevated persistently during the acute stages. The antistreptolysin titer and transaminase levels were normal.

A virus pathogenic for suckling mice was not isolated from the feces or plueral fluid. A titer rise of serum neutralization antibody for Coxsackie virus, group B, type 4 was demonstrated, as shown in table 3.

Case 2. A four year old boy developed "flu," manifested by fever, headache, malaise, nasal congestion, pharyngitis and nausea. Anterior chest pain, accentuated by breathing, and a pericardial rub were noted seven days later. The clinical course was moderately severe, with fever, tachycardia, tachypnea, pneumonitis and cardiomegaly. ST segment depression of the limb lead and inverted T waves were regarded as nonspecific. These electriocardiographic abnormalities returned to normal in three months. Recovery was complete. The highest blood leukocyte count was 5,050 per cubic millimeter, and repeated ASO titers were negative. Tests for cold agglutinins, HI antibody for influenza and adenovirus infection were negative. The highest titer of serum neutralizing antibody for Coxsackie virus, group B, type 2 was 320.

TABLE 3

Results of Coxsackie Serum Neutralization Tests in Case 1 (Pericarditis)

Day of Disease	B1	B2	B3	B4	B5
10	<5	<10	<5	160	<5
39	<5	<10	<5	640	<5
120	<5	<10	<5	640	<5

Comment: Of 14 patients studied, we feel justified, on the basis of clinical and serologic evidence, in adding three examples of Coxsackie pericarditis to the currently growing list. The clinical diagnosis of acute pericarditis due to Coxsackie virus appears to be confirmed on the basis of a significant rise in titer of serum neutralization antibody to types B4 in two cases, and B2 in one. In three other patients with acute pericarditis, high single antibody titers of 320 or higher to Group B, type 2 were demonstrated. In two patients, serial specimens showed high titers (640 or higher) to B2, although the lack of early serum specimen precluded the opportunity to detect a titer rise. The latter five patients are regarded as possible examples of Coxsackie virus pericarditis. Six patients with the clinical syndrome of acute pericarditis failed to show any evidence of the presence of Coxsackie virus disease.

Isolation of specific virus from the pericardium in high titer and demonstration of a significant rise in titer of the appropriate serum antibody would be convincing evidence. So far, these criteria have not been fulfilled.

INFLUENZA PERICARDITIS ASSOCIATED WITH RHEUMATIC HEART DISEASE

The following case report demonstrates an unusual viral complication of rheumatic heart disease.

Case 1. A 15 year old boy developed carditis typical of rheumatic fever following a streptococcal infection and chorea at the age of six. Throughout the ensuing years he manifested classic signs of cardiac failure, with cardiomegaly and the electrocardiographic abnormalities of tachycardia, delayed conduction, right axis deviation, and ST and T wave changes indicative of a diffuse nonspecific process.

During his terminal weeks the patient returned home briefly and contracted an infection thought to be influenza. The cardiac failure worsened, and a paradoxic pulse, Ewart's sign, and an increase in cardiac size were noted. Pericardiocentesis was performed on three occasions, with removal of serosanguineous fluid totaling 1,500 ml. Virus identified as Influenza A, Asian type, was recovered from the fluid in high titer. Cardiac decompensation continued, and the patient died suddenly.

The heart was dilated and weighed 500 gm. Fibrinous pericarditis was present. The myocardium showed a striking increase of the interstitial connective tissue, with extensive fibrosis and Aschoff bodies.

Comment: Pericarditis is an uncommon complication of influenza. However, Lucke[32] described five instances of serofibrinous or fibrinous pericardial reaction in 126 fatal cases of flu in 1919. The patient described above had severe rheumatic myocarditis. Late in the course, pericarditis with effusion developed as a feature of influenza. This undoubtedly hastened his death. Conceivably, the preëxisting heart disease predisposed to the pericardial complication by influenza virus. This is conjecture.

Discussion of Pericarditis

The association of Bornholm disease or epidemic myalgia and pericarditis was described in 1933.[54, 63] Although serologic and virologic technics were unavailable, the clinical findings in six patients indicated that benign pericarditis, with transient electrocardiographic changes, occurred in patients with this illness. Presumably, these patients had Cocksackie disease.

Coxsackie virus has been isolated from the pericardial fluid and from several stool samples of a 10 month old child with the clinical manifestations of acute pericarditis and myocarditis.[64] The virus strain was group A, type 3. It is of interest that the highest serum neutralization titer against the isolated srain was 1 : 20. In two patients studied independently, the clinical diagnosis of acute benign pericarditis seems plausible.[65, 66] Each showed diagnostic titers of neutralizing antibody to Coxsackie virus, group B, types 4 and 5, respectively. Movitt, Lennette and their associates indicted the Coxsackie viruses on a firmer basis.[56] In two patients, Coxsackie virus identified as group B, type 3 and as group A, type 1 was isolated from the feces. A rise of neutralizing antibody in the patient's serum against these strains was demonstrated in each instance. Virus was not recovered from pericardium removed by biopsy on approximately the nineteenth day of disease. Lennette and his group reported the findings of seven patients with pericarditis associated with pleurodynia.[67] Coxsackie virus was isolated from the stool in one patient. In this series a significant titer rise was demonstrated in one case, although high single titers were demonstrated in

three patients. A recent report described the clinical manifestations of pericarditis, the isolation of Coxsackie virus, group B, type 3, and a significant rise in titer of serum neutralization antibody in a laboratory worker exposed to that virus.[68]

Examples of specific types of pericarditis, especially Coxsackie virus pericarditis, are now recognized with increasing frequency, and the application of modern laboratory technics will provide additional clues to the nature of the unidentified group.

When acute viral pericarditis is manifest in its clinically isolated form, it is usually benign. Clinicians must be aware that pericardial involvement is not always the sole abnormality, since there may be associated myocarditis and transient myocardial embarrassment.

Conclusions

Specific examples of myocarditis occurring in two infants and in one adult during the course of Coxsackie disease are presented. Myocarditis associated with influenza, poliomyelitis and Rocky Mountain spotted fever is described.

Eight examples of Coxsackie virus pericarditis are reported, with clinical descriptions of two cases. The diagnosis is based on serologic findings.

Influenza virus, Asian type, was recovered from the pericardial fluid of a patient whose chronic rheumatic carditis was complicated by the development of serofibrinous pericarditis.

Myocarditis and acute benign pericarditis are reviewed briefly. Possible mechanisms leading to chronic myocarditis are discussed.

Acknowledgment

Keen appreciation is expressed to Dr. Anthony Perlman, Dr. Harold E. Harrison, Dr. Milton Markowitz, Dr. Paul F. Guerin and Dr. Guido Robino for allowing us to report the clinical findings of patients under their care. We are indebted to the resident staff of the University Hospital and the technical staff of the Division of Infectious Diseases for performing the clinical and laboratory studies pertaining to the patients. Dr. Merrill J. Snyder was particularly helpful. Dr. Lester Kiefer and Dr. Thomas J. Burkart, Assistant Professors of Pathology, interpreted the histologic sections and aided in their preparation.

Summario in Interlingua

Myocarditis e pericarditis es clinicamente importante. Il existe numerose agentes microbial de action specific—incluse recentemente characterisate typos de virus—que causa acute pericarditis benigne e que attacca le myocardio in particular.

Es presentate exemplos specific de myocarditis occurrente in duo infantes e in un adulto durante le curso de morbo a Coxsackie. Recente reportos concernite con iste disordine es summarisate brevemente. Myocarditis associate con influenza, poliomyelitis, e febre del Montanias Roccose es describite. Le numerose formas infective de myocarditis es mentionate, e le thema es revistate brevemente. Es opinate que multe casos de morbo cardiac non-valvular ha possibilemente lor inception in lesiones acute del myocardio le quales appare primo durante le curso del un o del altere acute processo infectiose. Ben que le manifestationes clinic de myocarditis

es usualmente transiente e reversibile, il es ben plausibile supponer que le concomitante alterationes tissular pote preparar le terreno pro le florimento de pre-existente o nove disveloppamentos pathologic. Mechanismos possibile es describite.

Es reportate octo exemplos de pericarditis a virus Coxsackie. Descriptiones clinic es includite pro duo del casos. Le diagnose es basate super constatationes serologic. Virus de influenza (typo asian) esseva retrovate in le liquido pericardial de un patiente in qui un chronic carditis rheumatic esseva complicate per le disveloppamento de pericarditis serofibrinose.

Le litteratura de data recente pertinente a pericarditis per virus Coxsackie es presentate.

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ENVIRONMENTAL TREATMENT OF A HEREDITARY ILLNESS: WILSON'S DISEASE*†

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Introduction

Wilson's disease is the outcome of the interaction of an inherited defect and the environment. The inherited defect is an inability to synthesize a normal amount of the normal plasma copper-protein, ceruloplasmin.[1] This is the consequence of the autosomal inheritance of one abnormal gene from each parent of the patient.[2] The environmental factor is copper,[3] and the interaction of inheritance and environment appears to result in the retention of abnormally large amounts of dietary copper.[4, 5, 6] This copper is deposited in several organs, and seems ultimately to produce pathologic effects, most prominently in the brain, where degeneration, though widespread, is most marked in the basal ganglia;[7] in the liver, where postnecrotic cirrhosis eventuates;[8] in the kidney, where tubular and glomerular dysfunction results;[9] and in the eye, where pathognomonic corneal copper deposits are known as Kayser-Fleischer rings.[10]

Several other diseases are known which also result from the interaction of a genetic defect and the environment. Two examples are (1) agammaglobulinemia,[11] and (2) galactosemia,[12] where the genetic defect and environmental factor are, respectively, (1) marked deficiency of normal gamma globulins, and bacterial infection in agammaglobulinemia, and (2) deficiency of phosphogalactotransferase, and galactose in galactosemia. The treatment of each of these diseases is fundamentally different: (1) replacement of gamma globulin by its periodic intramuscular injection into agammaglobulinemic patients, and (2) the elimination of galactose from the diet of a galactosemic patient. Thus, agammaglobulinemia is treated by correcting the result of the hereditary defect, and galactosemia is treated by removing galactose from the environment. This paper presents evidence to show that replacement of ceruloplasmin is not effective therapy in Wilson's

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disease, and that modification of the environment is consequently the only available treatment.

Ceruloplasmin as Treatment of Wilson's Disease

Ceruloplasmin is a blue globulin with a molecular weight of 151,000, eight copper atoms per molecule, and the ability to catalyze the oxidation of certain polyamines and polyphenols.[13] It is normally present in human plasma at a concentration of about 30 mg. per 100 ml., though this rises in pregnancy and many disease states.[14] A lower-than-normal concentration is found transiently in newborn infants and in a few illnesses, but marked and permanent deficiency is seen only in patients who have or will eventually develop Wilson's disease.[14]

The function of ceruloplasmin is not known with certainty. But the fact that chronic copper toxicity—Wilson's disease—occurs only in the face of its marked deficiency suggests strongly that the role of ceruloplasmin is intimately related to the regulation of absorption, excretion and/or deposition in tissues of copper.

Table 1

Characteristics of Ceruloplasmin CH-121

Protein mg./ml.	Copper Content μg./ml.	Purity (Electrophoretic)	Blue Color[15] $\Delta O.D._{1\ cm}^{610\ m\mu}$	Enzymatic[15] Activity $\Delta O.D._{1\ cm}^{540\ m\mu}$/min.
21.9	60.5	67%	1.085	1.315

To determine the effects of elevating the concentration of ceruloplasmin in patients with Wilson's disease to normal, a purified, concentrated preparation of the protein was made from human plasma.* Some characteristics of this ceruloplasmin are found in table 1. Intravenous administration of this lot of ceruloplasmin to two control subjects resulted in no fever, tachycardia, alteration in blood pressure or any other untoward effects. It had been heated to 60° C. for 10 hours during preparation, and no hepatitis developed in recipients. Two patients with Wilson's disease were given enough of the protein to raise their plasma concentration of ceruloplasmin to the normal range.[16]

The first patient, D. S., a woman of 24, had suffered from Wilson's disease for five years, with characteristic Kayser-Fleischer rings, and neurologic, hepatic and renal manifestations. Whenever determined, her plasma had always shown less than 1 mg. of ceruloplasmin per 100 ml. She

* Through the coöperation of Sam T. Gibson, Director, American National Red Cross Blood Program, and James A. McComb, Director, John M. Newell and Lewis H. Larsen, of the Biological Laboratories Department of Public Health of the Commonwealth of Massachusetts, we obtained Cohn fraction IV-1 from human plasma. Ceruloplasmin CH-121 was prepared from fraction IV-1 under the direction of Dr. H. O. Singher, of the Ortho Research Foundation, Raritan, New Jersey.

was given 1.36 gm. of ceruloplasmin CH-121 intravenously, over 100 minutes, with no febrile, hypotensive or other toxic reaction.

The second patient, G. G., a girl of 18, first developed overt Wilson's disease at the age of 13. She, too, had Kayser-Fleischer rings, and typical neurologic, hepatic, and renal symptoms and signs. She has had less than 1 mg. of plasma ceruloplasmin per 100 ml. on all measurements. Intravenously, 1.35 gm. of ceruloplasmin CH-121 were given to her, and there was no toxic reaction of any kind.

The observations made following ceruloplasmin administration to these two patients are summarized in table 2, and relate to:

1. Half-life of the protein.
2. Effects on copper absorption and/or excretion.
3. Effects on metabolism of copper^{64}.
4. Clinical effects.

TABLE 2

Observations Following the Oral Administration of 2.0 mg. of Cupric^{64} Ion Before and After the Intravenous Infusion of Purified Human Ceruloplasmin to Two Patients with Wilson's Disease

	D. S.		G. G.	
	Pre-infusion	Post-infusion	Pre-infusion	Post-infusion
Serum concentration of ceruloplasmin (mg./100 ml.)	<1	27	<1	29
Half-life of ceruloplasmin (days)	—	5.6	—	7.2
% of orally administered copper^{64} acetate removed in 4 days in				
Stool	42.9	41.0	20.1	32.4
Urine	0.43	2.42	0.77	0.53
Clinical effects		None		None

These results indicate that ceruloplasmin produced a concentration of greater than 15 mg./100 ml. for over four days in the first patient, and for over five days in the second. Figure 1 shows the relative ceruloplasmin concentration of D. S.'s plasma on a logarithmic scale as a function of time, from which the half-life of ceruloplasmin was calculated by the method of least squares. The results of the study in the second patient G. G. were similar. There was no effect on stool or urine excretion of oral cupric^{64} ions compared to the control values in the first patient, and an effect in the second patient considerably less than the fluctuations seen in repeated balance studies in one individual. In marked contrast to a control subject (figure 2), no cupric^{64} ion entered ceruloplasmin in the first patient (figure 3A), even when her concentration of this protein was 25 mg./100 ml. (figure 3B). Results of this study were the same in the second patient. No clinical effects, beneficial or otherwise, were seen in the control subject or in either patient.

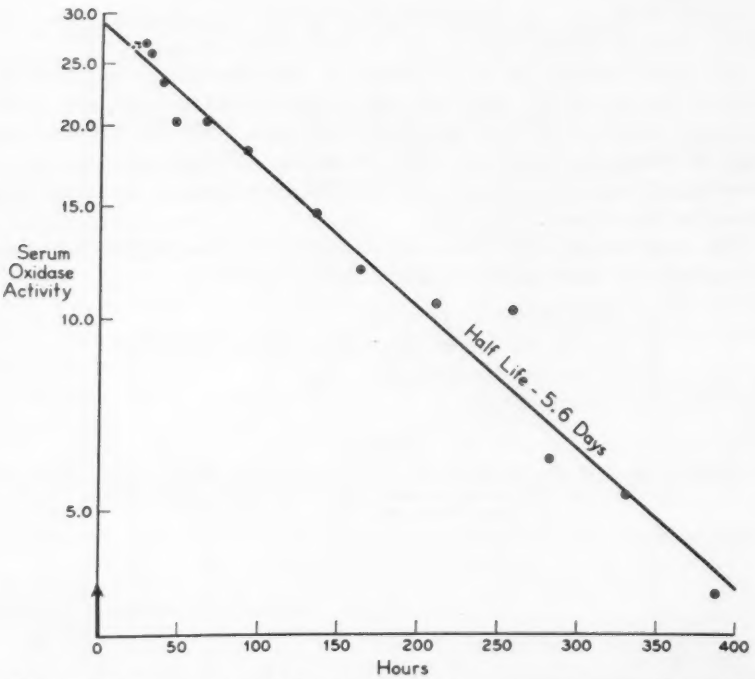

FIG. 1. Relative serum ceruloplasmin concentrations, measured as oxidase activity, following intravenous infusion of 1.36 gm. of purified human ceruloplasmin into a patient with Wilson's disease (D. S., ♀, 24). Scale of ordinate is logarithmic.

It is worth pointing out that the lack of incorporation of copper^{64} into ceruloplasmin in these patients seems to be particularly significant, since it is unlikely that ceruloplasmin can alter the metabolism of copper unless the metal is incorporated into the protein. Incorporation of copper can occur,

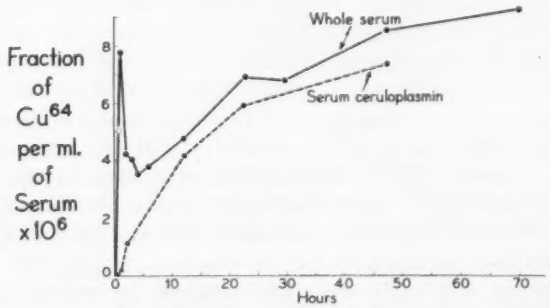

FIG. 2. Concentration of copper^{64} in whole serum and serum ceruloplasmin following oral administration of 2 mg. of cupric^{64} ion in a control subject (W. K., ♂, 67), with a concentration of ceruloplasmin in serum of 29 mg./100 ml.

theoretically, during synthesis of ceruloplasmin, or by exchange of cupric[64] ions with preëxisting ceruloplasmin copper.[17] The experiment carried out in the absence of ceruloplasmin suggests that incorporation during synthesis of ceruloplasmin does not occur, and the experiment performed when the plasma concentration of ceruloplasmin was normal suggests that incorporation by exchange does not occur in patients with Wilson's disease.

It is possible that infusion of a copper-free, undenatured derivative of ceruloplasmin—that is, apoceruloplasmin[18]—might be expected to alter

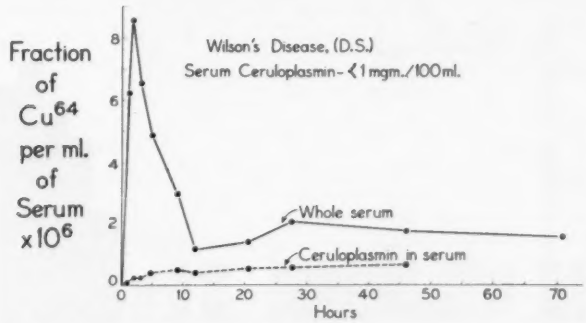

FIG. 3A. Concentration of copper[64] in whole serum and serum ceruloplasmin following oral administration of 2 mg. of cupric[64] ion in a patient with Wilson's disease (D. S., ♀, 24) with a concentration of ceruloplasmin in serum of less than 1 mg./100 ml.

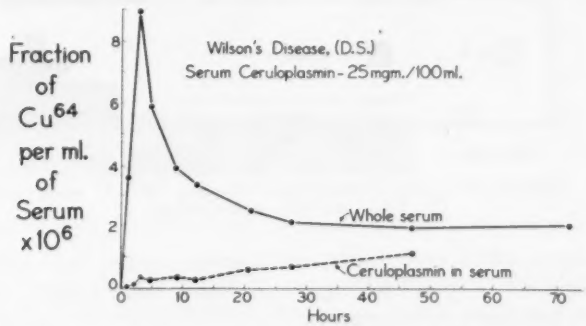

FIG. 3B. Concentration of copper[64] in whole serum and serum ceruloplasmin following oral administration of 2 mg. of cupric[64] ion in a patient with Wilson's disease (D. S., ♀, 24) whose concentration of ceruloplasmin in serum had been raised to 25 mg./100 ml. by the administration of 1.36 gm. of purified human ceruloplasmin one day previously.

favorably these metabolic variables in patients with Wilson's disease, but apoceruloplasmin suitable for human administration has not yet been made available.

Bickel and his collaborators[19] have obtained results similar to ours, in that they have found no clinical benefit following ceruloplasmin administration to three patients with Wilson's disease.

Thus, direct correction of the hereditary deficiency of ceruloplasmin in patients with Wilson's disease appears to be without effect on those features of the disease which one would like to correct. All that is left to offer the patient at present, then, is environmental treatment.

Environmental Treatment of Wilson's Disease

Copper in the external environment—the diet—may be reduced by selection of foods * which contain little copper, and by the oral administra-

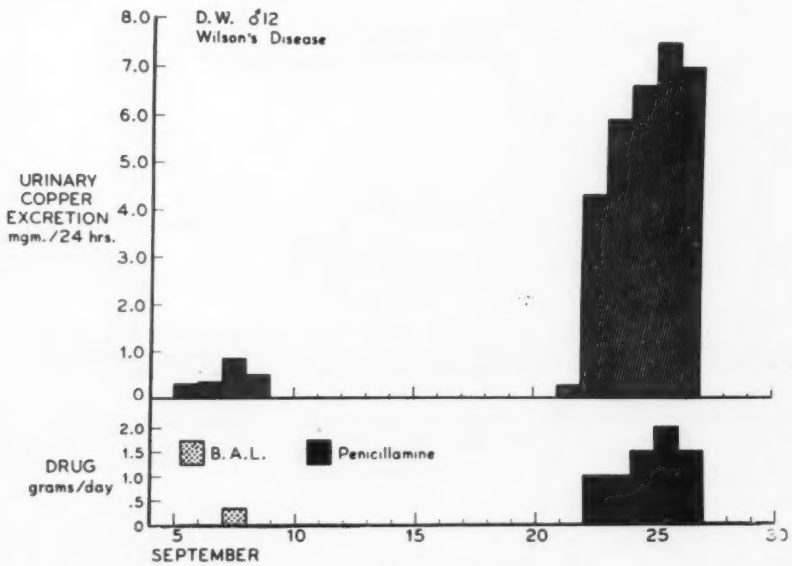

Fig. 4. Cupriuria in a patient with Wilson's disease with (1) no medication, (2) BAL, and (3) penicillamine.

tion of an agent which precipitates, and thereby renders unabsorbable, the copper in the diet. Cation exchange resins [6] and, more recently, potassium sulfide [5] have been used as such agents.

Copper already deposited in tissues—in the internal environment—can be removed by the use of chelating agents like BAL (2,3-dimercaptopropanol)[20] or penicillamine (β,β-dimethylcysteine),[21] which combine with copper and permit it to be excreted in the urine.[22-30] Figure 4 shows the magnitude of the cupriuria which reasonable doses of these drugs can induce, in comparison to the excretion of copper in the absence of the drug. As much as 7 mg. of copper—or about 10% of the total body copper of an adult—can be excreted in one day. Unfortunately, in patients with Wilson's disease

* A low-copper diet can be obtained on request to the authors.

the efficacy of the drug diminishes as its administration is continued, as is seen in figure 5, but *some* copper can apparently always be removed.

Our present regimen,[30] which combines these two aspects of the environmental treatment, consists of the following, continued indefinitely:

1. A low-copper diet.
2. Potassium sulfide, 40 mg. with each meal.
3. Penicillamine, 1 to 4 gm. daily in divided doses.

The penicillamine dosage is adjusted upward if the 24-hour urinary excretion of copper falls below 1 mg. Toxicity due to penicillamine has been seen, including fever, skin rash, leukopenia and thrombocytopenia, but has

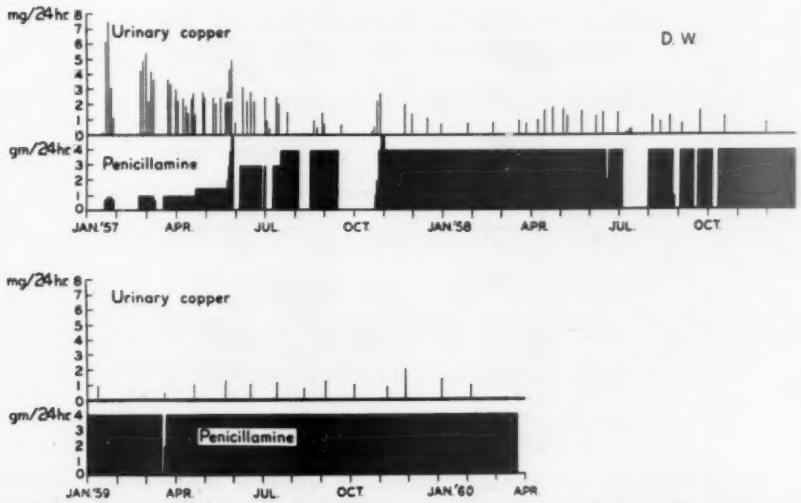

FIG. 5. Effect on cupriuria of three and one quarter years of penicillamine administration.

never been severe enough to require more than transient withdrawal of the drug, or temporary administration of steroids. Iron deficiency can be produced by this regimen, but can easily be prevented by the administration of ferrous sulfate one day a week, without potassium sulfide or penicillamine.

The results of this slow but steady "de-copperizing" procedure confirm the fact that the copper deposits in the tissues are diminished, and suggest that this diminution is of at least some benefit to the patient.[30]

That copper deposits are diminished by this regimen is evident in two patients where prominent Kayser-Fleischer rings virtually disappeared under this regimen. Information bearing on the diminution of hepatic copper deposits is scant. In one boy who has no detectable concentration of ceruloplasmin, and whose aceruloplasminemic older sister has severe Wilson's

disease, a liver biopsy at three and one-half years was found to contain 1,092 μg./gm. of dry weight. This decreased, after a year of therapy essentially the same as that given above, to only 944 μg./gm., hardly a striking change. Data of this kind relating to other tissues do not exist.

Clinically, the disappearance of Kayser-Fleischer rings is of little import, since the rings produce no visual impairment. Liver function has been improved quite clearly in only one patient, D. S., of figure 6, in whom several years of amenorrhea have ended, and spider angiomata and bouts of abdominal pain have decreased markedly on treatment. In the other patients depicted in figure 6, no appreciable change in liver disease has been noted.

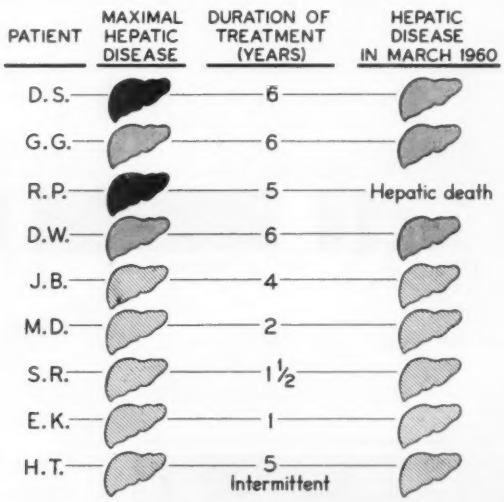

FIG. 6. Effect of "de-copperizing" treatment on severity of hepatic disease, estimated by clinical and laboratory criteria, in nine patients with Wilson's disease. Blackness of liver sketch is roughly proportional to severity of liver disease.

Neurologic improvement definitely results from treatment, as is summarized in figure 7, although several patients have shown initial transient worsening. An example of what we mean by improvement is the case of G. G. This girl almost had to withdraw from high school four years ago because of tremors, rigidity, drooling and emotional instability, which developed rapidly after an acute paralytic onset of the illness. On intensive therapy she improved so markedly that she was graduated from high school with her contemporaries and was voted the "most improved athlete" in her class. She now has a part-time job and is considering marriage. Not all of our gratifying results are clearly related to therapy, however. H. T., a woman of 47, seems on therapy to have shown a neurologic worsening which, unlike the temporary exacerbation following institution of therapy in other

patients, was prolonged and progressive. She improved markedly—from being unable to walk, to taking shopping trips from the Bronx to Manhattan herself—after all treatment was discontinued! Therefore, because of such occasional spontaneous remissions, caution is necessary in evaluating therapy.

We conclude that, in Wilson's disease, diet, potassium sulfide and penicillamine, or BAL, all directed toward minimizing copper in the environment, are chemically effective and clinically beneficial, but such treatment is not ideal in either respect.

Although neurologic improvement has been striking, several intensively treated patients, of ours and of others,[31] have died of liver disease. This is

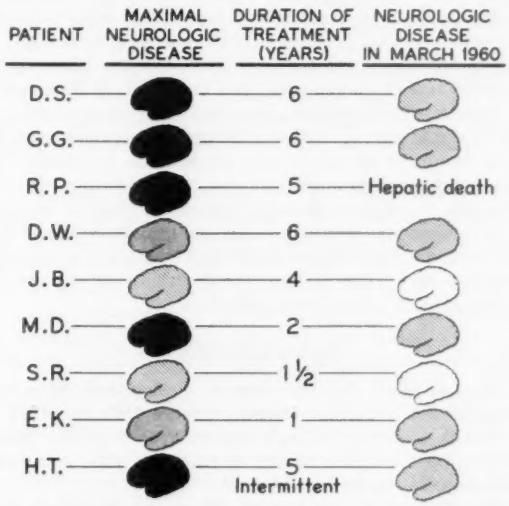

FIG. 7. Effect of "de-copperizing" treatment on severity of neurologic disease, estimated clinically, in nine patients with Wilson's disease. Blackness of brain sketch is roughly proportional to severity of neurologic disease.

not surprising, in view of the grave histologic and functional damage which the livers of these patients often exhibit when they are first diagnosed and treated. Consequently, it seems to be of the greatest importance to diagnose potential patients long before they become symptomatic—and simple screening tests [32, 33] are available to do this—and to begin environmental treatment when they are less than a year old.

SUMMARY

Wilson's disease is the result of the interaction of an inherited defect, manifested by an inability to synthesize normal amounts of normal ceruloplasmin, and an environmental factor, copper. Since the apparent effects of the inherited defect cannot be corrected by the administration of exogenous

ceruloplasmin, therapy can be directed only at the environment. The results are reported of treating 10 patients with Wilson's disease with a regimen which decreased the intake of copper and promoted the excretion of the metal already deposited in the tissues.

SUMMARIO IN INTERLINGUA

Le morbo de Wilson es le resultato del interaction de un defecto hereditari con factores del ambiente. Le defecto hereditari se manifesta in le incapacitate del corpore de synthetisar quantitates normal del normal proteina a cupro, ceruloplasmina, e le factores ambiental es illos del provision de cupro. Patientes con morbo de Wilson, o subjectos destinate a disveloppar morbo de Wilson, absorbe e/o retene excessive quantitates de cupro dietari, con le resultato de depositos pathologic de cupro in varie organos del quales le cerebro, le hepate, e le renes es le plus importantes. Ben que le reimplaciamento del proteina specific que es geneticamente inadequate se ha monstrate therapeuticamente efficace in le caso de certe altere morbos hereditari, le infusion de ceruloplasmina in patientes con morbo de Wilson non pare producer ulle alterationes benefic o clinicamente apparente. Per consequente le therapia pote visar solmente al ambiente per (1) reducer le ingestion e absorption de cupro dietari e (2) promover le excretion del cupro jam deponite in le tissus. Un tal regime—utilisante un dieta a basse contento de cupro e le administration de sulfuro de kalium e de penicillamina—ha reducite le depositos de cupro tissular in concomitantia con marcate grados de melioration neurologic sed sin grande beneficio quanto al morbo hepatic. Es sublineate le importantia de deteger subjectos aceruloplasminemic pro prevenir—per le uso de un regime del typo hic describite—le deposition de cupro ante le declaration de irreversibile alterationes pathologic.

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UNEXPECTED DEATH IN BRONCHIAL ASTHMA: A WARNING SIGN WITH A CLINICOPATHOLOGIC CORRELATION *

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DEATH in uncomplicated bronchial asthma is a shocking experience. Recently such a death at this hospital provoked an inquiry into the cause of such fatalities and their possible prevention.

A study of the autopsy files from 1933 to 1960 produced records of three asthmatic deaths, which occurred in 1948, 1955, and 1959. These three patients died quite unexpectedly during acute attacks of extrinsic asthma. Other deaths attributed to bronchial asthma were not included in this study because of the presence of concurrent disease processes, such as cardiac or infectious pulmonary involvement, or because such deaths occurred in the older age groups, where sudden death without significant pathologic findings is not unusual.

The three cases reported here are unique in several aspects: (1) the patients were in the younger age group;[1-4] (2) no concomitant disease process was present;[5] (3) all had extrinsic asthma, in which fatalities are exceedingly rare;[3, 6, 7, 8] (4) each showed a similar clinical picture just prior to death; and (5) postmortem pathology was the same in each case.

This paper will outline a clinical picture which is a poor prognostic sign, and correlate it with the findings present at autopsy.

CASE REPORTS

Case 1. This 44 year old white male was admitted with a severe asthmatic attack, precipitated by the arrival of redecorated chairs in his home. Prednisolone inhalers, adrenalin in oil, ACTH and aminophylline had been tried unsuccessfully before admission. He had a 17-year history of seasonal asthma, and had been found to be sensitive to grasses and ragweed. Desensitization courses and the occasional use of steroids had kept him free from severe attacks until three months prior to this admission. At that time he had been hospitalized for seven weeks with status asthmaticus. He was then adequately controlled on steroids and potassium iodide until his final admission.

Physical Examination: The patient was a well developed, well nourished white male in acute respiratory distress, using the accessory muscles of respiration. Blood pressure, 140/80 mm. of Hg; pulse, 140 and regular; respiration, 20, but labored; temperature, 98.4° F. Positive findings were limited to the chest: the lungs were hyperresonant, and inspiratory and expiratory wheezes were heard over the entire

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lung fields. An electrocardiogram showed sinus tachycardia. The chest film was negative.

Course in Hospital: The patient received barbiturates, ACTH and aminophylline intravenously. Nasal oxygen and a neo-synephrine nebulizer were also used. On this regimen he improved both subjectively and objectively. However, on the fifth day he developed severe dyspnea. This was temporarily relieved by aminophylline, but it recurred and, despite therapy, he continued to complain of shortness of breath. Several observers could hear no rhonchi or wheezes, and the dyspnea was thought to be due to apprehension. On the day prior to death, adrenalin was given, with symptomatic relief for several hours. However, on the morning of the ninth day the patient was found to have severe air hunger. He turned cyanotic, and died within 10 minutes.

Comment: This patient had documented extrinsic asthma and a history of one almost-fatal attack following the petting of a rabbit. Several observers thought that the dyspnea which he exhibited with an apparent improvement in lung findings—that is, a decrease in wheezing—was due to a psychosomatic overlay. Necropsy findings showed an organic basis for his complaints.

Case 2. This 17 year old white female, a known asthmatic, had developed severe dyspnea five hours before admission. She had had asthma since infancy, with attacks increasing in frequency and intensity until they had been occurring about three times a month during the last two years of her life. There had been three recent hospitalizations for these episodes. At the allergy clinic she was found to be sensitive to many allergens, including cat dander, but she refused to be separated from her cat. Desensitization was not attempted. Her grandfather, father, and brother had bronchial asthma.

Physical Examination: The patient was a well developed, poorly nourished white female in marked respiratory distress. Blood pressure, 110/80 mm. of Hg; pulse, 140; respiration, 40; temperature, 98.4° F. The rest of the physical examination was negative except for the presence of noisy, rapid respirations, loud inspiratory and expiratory wheezes over the entire lung fields, and prolonged expirations. An electrocardiogram showed sinus tachycardia; the chest film, increased bronchovascular markings.

Course in Hospital: The patient was given sedation, an intravenous drip of ACTH, and oxygen by nasal catheter and later by tent. Demerol, adrenalin, and aminophylline were given, with but little improvement in the clinical picture. Although the patient was afebrile, Aureomycin was added to the regimen. After 60 hours she showed signs of objective improvement, in that the wheezes were not heard despite an increased respiratory rate. Ten hours later she suddenly began to gasp, turned cyanotic, and died.

Comment: This patient also had extrinsic asthma. She was in status asthmaticus for 70 hours. Two hours prior to death, the physician's notes stated that auscultation of the lungs showed improvement—that is, wheezes had decreased, but dyspnea had increased. Because of this paradoxic finding, heart failure was considered and digitalization commenced. No note was made about the volume of breath sounds.

Case 3. This four year old white female was admitted to the hospital in marked respiratory distress. Her parents stated that two days earlier she had developed a sore throat without a fever, and 14 hours prior to admission had wakened complain-

ing of shortness of breath and abdominal pain. The dyspnea had become progressively worse during the course of the day.

The child's medical history revealed that she had had eczema until the age of two, at which time she had her first attack of asthma. Although she had had only one other severe attack, wheezing usually accompanied upper respiratory infections. The patient had been followed in an allergy clinic and been found to be sensitive to many allergens. There was no record of desensitization, and no family history of allergy.

Physical Examination: The patient was a well developed, poorly nourished child in acute respiratory distress. The skin was ashen grey, and the lips were intermittently cyanotic. All accessory muscles of respiration were in action. The patient was afebrile. The essential findings were limited to the throat and lungs. The tonsils were moderately enlarged, and there was a right tonsillar exudate. Prolonged inspirations and stertorous expirations were heard over the lung fields. Breath sounds were variable: occasionally they were distant, at other times noisy. Typical wheezing was not present. A second observer noted absent breath sounds over the left lower lung field.

FIG. 1. Large, voluminous lungs as they appeared in chest cavity.

Course in Hospital: The patient was given adrenalin immediately (7:15 p.m.), and later a Benadryl-aminophylline-phenobarbital compound, without improvement. She received penicillin, and was placed in an oxygen tent. Her color improved and she fell asleep. At 3:15 a.m. she was crawling about in the crib and appeared to be

comfortable. One hour later, however, while the nurse was taking her temperature, she ceased to breathe and turned cyanotic. Immediate resuscitative methods were of no avail, and she was pronounced dead nine and one-half hours after admission.

Comment: This child's entire course spanned only 24 hours. There was no evidence of infection either clinically or at post mortem. The admitting physician noted specifically the stridor without wheezing, and the variable intensity of the breath sounds.

FIG. 2. Large mucus plug occludes major bronchus.

PATHOLOGY

The pathology was almost identical in each patient. When the chest cavity was opened, the lungs were found to be voluminous, pale, and distended *in situ*. Rib indentations were present. The pleural cavities were clear, and no adhesions were noted. When the bronchial tree was opened, marked edema of the mucosa and mucus plugs in many of the segmental and subsegmental bronchi were seen. In case 2 a large mucus plug occluded the left main stem bronchus. Examination of the hearts was negative, with no generalized or specific hypertrophy (figures 1, 2, and 3).

Microscopically, the picture was similar. In no case was there any evidence of purulent infection. The most prominent cellular response was

round cell and eosinophilic. The most characteristic findings (figure 4) were:

1. Mucus plugs in the segmental and subsegmental bronchi and in the bronchioles.
2. Lymphocytic and eosinophilic infiltration of the mucosa and submucosa.
3. Hyperplasia of the mucous glands.
4. Hyalinization and thickening of the basement membrane.
5. Minimal to moderate hypertrophy of the bronchiolar musculature.
6. Alveolar emphysema.

Unger [1] states that there are no absolute diagnostic postmortem findings of asthma—that is, a pathologic diagnosis is rarely made unless it is clinically supported. However, all cases of sudden death due to asthma had findings similar to those reported above.[1-5, 9] Minor differences were noted in the cases reported here. There was no striking eosinophilic infiltration, no decrease in cilia, and no squamous metaplasia, as reported by some.[5]

The heart weights (340, 210, and 80 gm., respectively) were within normal limits for the age groups. Hypertrophy was not present, and in case 1

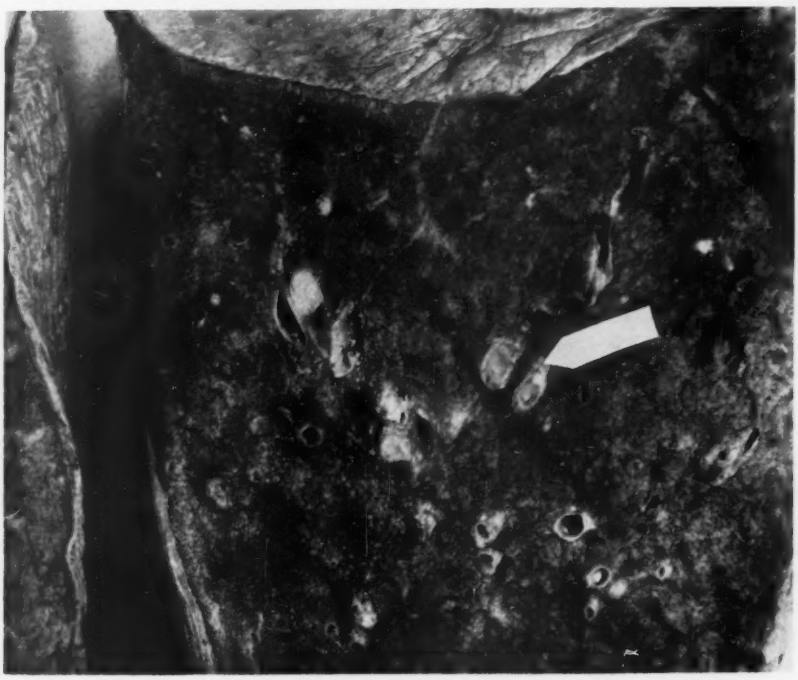

FIG. 3. Segmental bronchi are occluded by mucus.

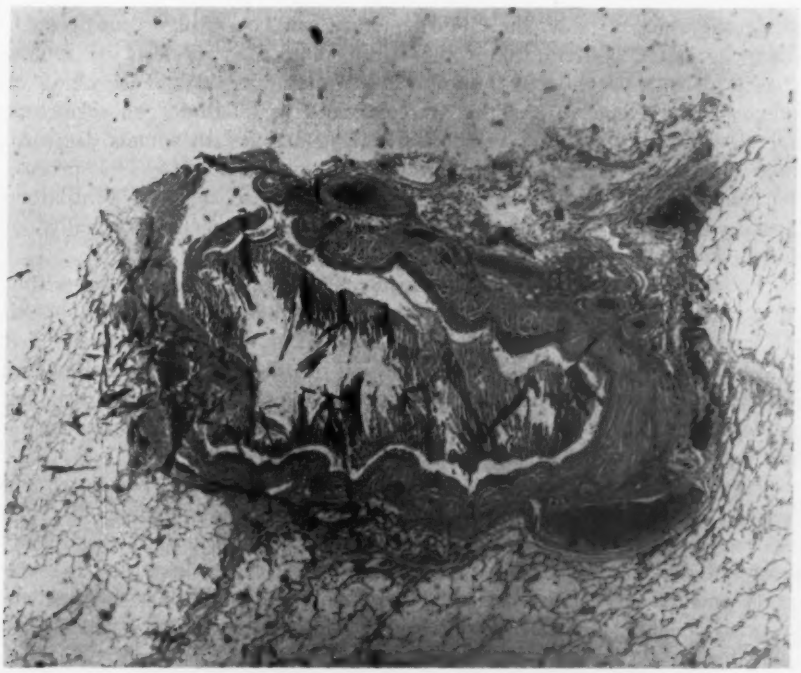

FIG. 4. Microscopic view of subsegmental bronchus occluded by mucus.

only minimal coronary arteriosclerosis was present. Clinically, as well as by electrocardiogram and chest film, these hearts were normal in size, shape, and function. This bears out Bullen's statement that asthma, unless complicated by chronic emphysema, does not damage the heart.[7, 10]

DISCUSSION

The most striking clinical feature noted in reviewing these three cases was the consistent observation of apparent auscultatory improvement just prior to death. The attending physicians in each case noted the decrease or disappearance of wheezing, despite increasing dyspnea. Only in case 3, however, did the clinician note the more important finding, that is, the decreased volume or absence of breath sounds. In the light of the autopsy findings, it is improbable that this change in breath sounds was not present in the other cases as well. It is understandable that the physicians were more impressed by the more obvious disappearance of wheezing. It is suggested that, if the triad of decrease in wheezing, increase in dyspnea, and decrease in breath sounds had been recognized, the pathophysiology would have been appreciated and appropriate measures instituted to prevent death.

At the autopsy table, the clinical picture can be readily reconstructed. The progressive obliteration of the minor pulmonary radicles by mucus plugs leads to a decrease in the number of functioning alveoli, resulting in compensatory dyspnea. As the muscular and cartilaginous subsegmental and segmental bronchi are occluded, wheezing and breath sounds decrease, since air can neither enter nor leave the blocked channels. This process continues to involve more and more of the lung, so that the ventilatory capacity is severely reduced, and when a strategic bronchus is finally occluded, sudden asphyxia and death ensue.

The details of the individual management of these patients are not within the scope of this paper. Many therapeutic regimens have been proposed, and each has some controversial aspect.[11, 12] It should be emphasized that no one medication can be blamed for these deaths, unlike those elsewhere reported to have been caused by such agents as morphine, demerol, aspirin, iodides, and pentothal sodium.[1, 4, 5] No signs of acute respiratory depression or anaphylactic drug reaction were present in these cases.

However, it is thought that the use of certain drugs and measures, and the omission of others, might have contributed to the final outcome. Oxygen was administered in all three cases because of cyanosis, but wetting agents were not added. It has been noted that dry oxygen increases the viscosity and tenacity of the bronchial secretions, and it inhibits the tracheobronchial cilia.[11, 12] Demerol and barbiturates, although not markedly responsible for depressing the respiratory center in these patients, may have weakened the cough reflex directly, and sedated the patients to such a degree that they were unable to cough effectively. Adequate hydration and the use of expectorants, such as potassium iodide, might have loosened the bronchial secretions and prevented the formation of the plugs which eventually caused death.

The clinical picture of decreased wheezing, increased dyspnea, and decreased breath sounds indicates a poor prognosis, and calls for a review of the therapy given. The following suggestions are offered:

1. Do not oversedate the asthmatic patient.
2. Encourage coughing and give expectorant help.
3. Use oxygen only if necessary, and then only in conjunction with a wetting agent.
4. Ensure adequate hydration.

If the patient's condition does not show rapid improvement, or if there is continued deterioration, then general anesthesia, preferably with ether,[5] should be given, and bronchoscopy with diligent aspiration performed. This may be life-saving.[4, 13]

Summary

1. Three cases of unexpected death in uncomplicated bronchial asthma are reported.

2. An important prognostic triad is described.
3. A clinicopathologic correlation is presented.
4. A course of therapy is suggested.

SUMMARIO IN INTERLINGUA

Morte subitanee in casos non complicate de asthma es inusual. Tres casos in que un tal morte occurreva durante acute attaccos asthmatic es discutite in le presente articulo. Le patientes esseva de juvene etates, habeva nulle concomitante processo pathologic, e lor asthma esseva extrinsec. Le tableaus clinic ante le morte esseva simile in le tres casos. In omnes le medico del servicio notava un reduction del sibilage asthmatic in despecto del crescente dyspnea. Esseva etiam notate que le sonos respiratori declinava o esseva absente.

Es postulate que iste triade—declino del sibilage, augmento del dyspnea, declino del sono respiratori—suggere un disfavorabile prognose e demanda un revision del therapia. Iste tableau clinic indica que le bronchiolos es blocate per buttones de muco e que le aere non pote passar in e ex le pulmon. Quando finalmente un broncho de function strategic es occlusionate, le patiente mori de asphyxia.

Le necropsias del presente casos monstrava le presentia de buttones de muco in le major e minor bronchos e bronchiolos.

Pro prevenir le occurrentia del mentionate triade, le suggestion es facite que le tractamento del patiente asthmatic debe includer un hydration adequate, adjuta de expectoration que promove le tusse, e le evitation de therapia a oxygeno e forte sedation. Si le triade es presente e le patiente deveni crescentemente dyspneic, bronchoscopia con aspiration del buttones de muco debe esser instituite.

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THE EFFECT OF THIAZIDE DIURETICS ON THE ABNORMAL KIDNEY * †

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Thiazide diuretics have been used with rather favorable results in the presence of renal disease.[1-4] Furthermore, several investigators [1, 4-7] have reported a low incidence of toxicity with the use of these drugs in patients with normal as well as with diseased kidneys. On the other hand, patients with liver disease and ascites appeared to be less responsive to these agents. Chlorothiazide, given to patients with cirrhosis, was associated with a reduction in serum potassium and a concomitant increase in the blood pH. Beyer [6] has demonstrated the effectiveness of chlorothiazide in the presence of both acidosis and alkalosis. Chlorothiazide will enhance diuresis by an exaggerated excretion of the preponderant ions (Cl or HCO_3). Hence, these agents may have certain homeostatic advantages over other diuretics in the presence of renal disease with secondary derangements of acid-base balance.

Schreiner [3, 4] was able to elicit a significant diuresis in 12 of 17 patients with the nephrotic syndrome. Failure of a diuresis in the other patients was attributed to azotemia, a marked reduction in the glomerular filtration rate, in filtered sodium load, or in serum albumin (values < 1.5 gm.). On the other hand, chlorothiazide given to patients with severe renal impairment due to chronic glomerular nephritis and chronic pyelonephritis effected very little change in weight, urine volume, or azotemia.

Because of the varied fluid and electrolyte responses, as well as the inconsistent reduction of blood pressure in hypertensive patients following thiazide diuretic therapy, it became apparent that renal factors were responsible for these discrepancies.

Methods and Materials

Seventeen studies were performed in 15 patients: six normal subjects, seven patients with moderately advanced hypertensive renal disease (glomerular filtration rate, 40 to 70 ml./min.), and two patients with severe

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renal impairment (glomerular filtration rate, < 40 ml./min.). Ten patients were infused with Ringer's solution, 10 ml./min., two of these receiving such infusions twice, and five patients were infused with 5% glucose in water, 10 ml./min., throughout the control and experimental periods. The experiments were so designed that the Ringer's-infused patients were receiving, excreting and reabsorbing an isotonic solution, whereas the glucose-infused patients were excreting a hypotonic urine prior to the injection of hydrochlorothiazide.

Following three 10-minute control periods, either 0.5 gm. chlorothiazide, 50 mg. hydrochlorothiazide, or 2 ml. meralluride was injected intravenously. Three to nine 10-minute experimental collection periods followed injection of the diuretic agent. Glomerular filtration rate (creatinine or inulin), renal plasma flow (para-aminohippuric acid), serum and urine sodium, potassium, total solutes, free water clearance, and uric acid were determined in accordance with methods previously described.[8]

Results

Acute Effects. In the normal subjects and in patients with only moderately advanced renal impairment, injection of intravenous thiazide diuretics elicited an immediate increase in osmolal clearance, urine flow and excretion of sodium, potassium and total solutes (figure 1). However, the patients with moderately advanced renal impairment (glomerular filtration rate, 40 to 70 ml./min.), and a maximal urine osmolal concentration of 600 to 800 milliosmols/Kg., exhibited an abbreviated diuresis with a relatively small increase in electrolyte and total solute excretion (figure 1). These increases occurred even though there was a tendency for a decrease in renal plasma flow, glomerular filtration rate, and the filtered load of sodium and total solutes (table 1).

Of the 12 patients receiving Ringer's solution, four demonstrated a decrease in free water clearance,* three an increase, and five showed no change. Substitution of an electrolyte-free (5% glucose in water) hydrating solution in five experiments demonstrated the same variability of solute and water excretion as that seen in the patients infused with Ringer's solution. (In two patients there was a decrease in C_{H_2O}, in two an increase, and in one no change; table 1.)

In the presence of advanced renal impairment (glomerular filtration rate, < 40 ml./min., and maximal urine osmolal concentration, < 600 milliosmols/Kg.), intravenous administration of hydrochlorothiazide, meral-

* Free water clearance, C_{H_2O}, is calculated as $C_{H_2O} = V - \left(\frac{U_{osm}}{P_{osm}} V\right)$.[12, 13] U_{osm} and P_{osm} represent urine and plasma total solute concentration as determined by the freezing point depression, using a Fiske osmometer. V indicates the urine flow in milliliters per minute. When the U_{osm}/P_{osm} ratio becomes greater than 1 (hypertonic urine), the free water clearance assumes a negative value and is then designated as $T^c_{H_2O}$. This value represents the nonobligated, solute-free water reabsorbed by the collecting ducts in concentrating the urine.

TABLE 1

Results of Intravenous Hydrochlorothiazide on Electrolyte and Water Excretion

Patient	Diagnosis	Hydrating Fluid	Renal Plasma Flow ml./min.	GFR† ml./min.	Urine Flow ml./min.	Serum Sodium mEq./L.	Serum Potassium mEq./L.	Serum Solute milliosmols/Kg.	Urine Solute milliosmols/Kg.	Potassium Excretion mEq./min.	Solute Excretion milliosmols/Kg. min.	% Excretion of Filtered Water	% Excretion of Filtered Na	% Excretion of Filtered Solute	Osmolal Clearance ml./min.	C_{H_2O}‡ ml./min.	BUN mg./100 ml.	Serum Uric Acid mg./100 ml.	Uric Acid Clearance ml./min.
1. J.E.	Normal subject	G/W*	C§ 561	145	4.8	143	3.7	308	227	49.0	133	5.9	1.3	0.5	4.2	0.6	34	6.3	18.5
			E_1 551	148	8.9	143	3.7	309	198	77.0	1,762	12.2	4.7	7.8	5.7	3.2	30	6.1	19.8
2. W.M.	Normal subject	Ringer's	C 202	88¶	2.1	139	3.9	300	309	13.8	65	2.4	1.1	1.2	2.4	−0.3	18	3.9	10.3
			E_1 442	118	5.8	140	4.0	295	311	23.4	180	4.4	2.0	9.0	4.2	−0.4	18	3.9	11.0
3 E.R.	Normal subject	Ringer's	C 607	119	1.6	136	3.9	310	501	76	79	1.3	1.2	2.2	2.5	−0.9	9	3.3	12.5
			E_1 701	119	3.3	137	3.9	300	395	123	130	2.8	5.4	3.6	4.3	−1.0	8	3.2	15.3
			E_2 703	69	3.5	136	3.9	311	481	136	168	5.1	13.0	7.8	5.1	−1.2	8	3.2	16.7
			E_3 658	75	4.2	137	3.9	311	497	125	209	5.6	16.0	9.0	6.7	−2.0	8	3.3	17.4
4. L.P.	Normal subject	Ringer's	C 312	113	5.7	141	3.9	317	255	105	298	5.0	1.1	4.1	4.6	1.1	26	6.2	8.6
			E_1 464	106	6.3	140	4.0	313	376	165	637	5.9	2.7	7.0	7.5	−1.3	26	6.2	9.1
			E_2 367	73	4.2	141	3.9	317	523	135	675	5.8	2.7	9.6	7.0	−3.0	26	6.2	7.1
5. C.B.	Normal	Ringer's	C 394	104	1.8	139	2.9	312	660	70	1,201	1.7	2.7	3.7	3.8	−2.0	29	5.8	12
			E_1 386	106	2.7	139	4.0	316	580	88	1,524	2.5	6.5	4.6	4.8	−2.1	29	5.8	23
6. J.P.	Normal subject	Ringer's	C 262	101	1.3	134	3.7	230	430	13.3	57	1.3	1.3	1.9	2.5	−0.8	19	4.0	10
			E_1 270	123	2.8	133	3.8	293	405	28.4	134	2.3	6.4	3.7	4.0	−1.8	16	4.0	11
7. F.M.	Hypertension	Ringer's	C 306	64¶	3.7	139	3.2	326	219	9.5	81	5.8	1.3	3.9	2.4	1.3	34	4.1	9.3
			E_1 308	64	3.6	140	3.2	305	393	26.1	140	5.6	5.3	7.2	4.6	−1.1	29	4.0	9.0

* G/W = 5% glucose in distilled water.
† I = Inulin.
‡ C_{H_2O} = Free water clearance. Negative values represent $T^c_{H_2O}$ or the amount of nonobligated, solute-free water reabsorbed.
§ Mean of three 10-minute control periods. This was followed by 50 mg. of hydrochlorothiazide.

TABLE 1 (*Continued*)

Patient	Diagnosis	Hydrating Fluid	Renal Plasma Flow ml./min.	GFR† ml./min.	Urine Flow ml./min.	Serum Sodium mEq./L.	Serum Potassium mEq./L.	Serum Solute milliosmols/Kg.	Urine Solute milliosmols/Kg.	Potassium Excretion mEq./min.	Solute Excretion milliosmols/Kg. min.	% Excretion of Filtered Water	% Excretion of Filtered Na	% Excretion of Filtered Solute	Osmolal Clearance ml./min.	C_{H_2O}‡ ml./min.	BUN mg./100 ml.	Serum Uric Acid mg./100 ml.	Uric Acid Clearance ml./min.
8. L.A.	Hypertension	Ringer's	C 571	73[1]	1.3	142	4.4	315	398	53	49	1.8	1.5	2.1	1.6	−0.2			
			E_1 356	65	4.7	141	4.3	304	297	37.6	120	7.2	2.4	6.1	4.3	+0.8			
9. J.P.	Hypertension	G/W	C 363	79[1]	9.8	135	3.5	313	313	26.5	240	12.4	3.0	8.6	7.8	4.6			
			E_1 319	66	14.3	136	3.5	306	217	46.7	313	21.7	8.0	15.1	10.2	4.6			
10. I.W.	Hypertension	G/W	C 418	110	6.9	140	3.3	307	91	39.0	628	3.1	1.4	1.8	3.1	3.8	21	6.2	11.1
			E_1 389	114	7.0	140	3.4	305	128	65.0	896	5.0	3.6	2.6	5.0	2.0	21	6.3	8.3
11.a R.K.	Hypertension	Ringer's	C 474	83	8.5	143	3.7	316	227	92.3	1,929	10.2	3.3	7.4	6.0	2.6	21	5.5	13.5
			E_1 430	116	8.5	143	3.7	318	363	140.0	3,085	7.3	8.6	8.4	9.6	−1.1	24	3.8	18.1
11.b R.K.	Hypertension	G/W	C 272	99	7.6	143	4.0	305	117	38.0	889	7.7	5.8	3.0	2.8	4.9	15	5.3	8.5
			E_1 580	70	4.6	140	4.0	306	327	99.0	1,504	6.6	6.6	7.1	5.0	−1.1	15	5.4	7.4
12. E.W.	Gout, hypertension	Ringer's	C 182	57	5.4	140	4.0	311	234	54.2	1,263	9.5	1.4	7.1	4.0	1.4	77	6.4	1.2
			E_1 163	51	6.2	140	3.9	308	260	80.0	1,612	12.1	1.1	10.2	4.6	5.7	75	6.4	1.3
13. S.C.	Hypertension	G/W	C 276	162	8.4	139	4.0	285	281	38.0	2,360	18.2	14.0	20.8	8.2	0.2	9	2.8	27.2
			E_1 236	166	10.5	139	3.9	282	288	46.0	3,024	21.8	21.1	22.3	10.6	−0.1	8	2.3	26.5
14.a V.R.	Chronic pyelonephritis	Ringer's	C 24.8	8.5	3.7	130	5.1	325	271	26.3	99	42.7	25.1	35.0	3.4	0.6	70	7.3	9.2
			E_1 21.0	11.0	4.1	130	5.1	323	330	29.7	133	37.6	28.2	37.8	4.2	−0.1	73	7.3	10.5
			E_2 15.0	8.7	3.6	129	5.0	315	291	22.3	104	41.4	37.1	39.1	3.3	0.3	71	7.3	9.6
14.b V.R.	Chronic pyelonephritis	Ringer's	C 31	7.1	3.1	130	5.2	332	245	25.3	76	43.7	20.0	31.0	2.3	0.8	135	7.5	4.7
			E_1 26	5.9	2.5	130	5.1	327	272	30.0	68	42.4	24.4	35.0	2.1	0.4	135	7.5	4.7
15. S.R.	Hypertension	Ringer's	C 149	30[1]	6.7	138	4.0	298	306	40.2	208	22.4	7.6	22.4	7.0	−.25	78	5.5	.93
			E_1 134	27	6.1	139	4.0	307	189	39.4	116	22.5	7.6	14.0	3.8	2.3	71	5.4	.80
			E_2 123	22	5.1	139	4.1	292	188	33	36	22	8.4	15	3.3	1.8	77	5.5	.64
			E_3 117	19	4.0	140	4.2	283	133	27	53	20	8.3	10.0	1.8	2.1	65	5.4	.48

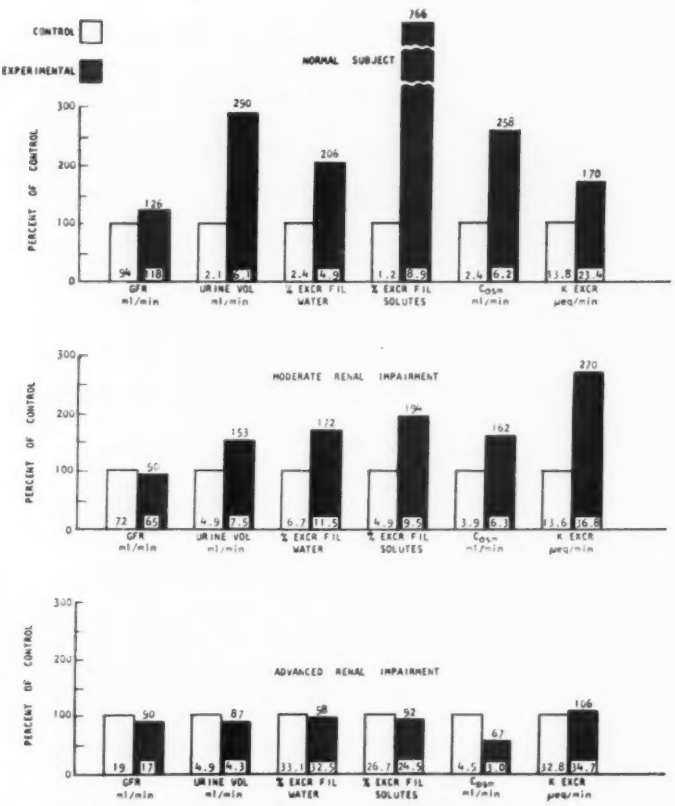

FIG. 1. Electrolyte and water response to intravenous hydrochlorothiazide in normal subjects and in patients with moderate and advanced renal impairment.

TABLE 2

Effect of Long-Term Administration of Thiazide Diuretics on Renal Function

	BUN mg./100 c.c.	GFR (C_{cr}) mL./min.	Maximal Urine Osmol Conc., millosmols/Kg.
Normal	<20	>100	>800
D_1 Mean	16.8	69.1	700
SD	±4.8	±5.3	±62.1
SE	±1.3	±1.9	±14.0
D_2 Mean	17.0	61.0	703
SD	±5.3	±6.9	±50.0
SE	±1.5	±3.1	±12.9

D_1 = Pretreatment.
D_2 = Following therapy (mean, 6.6 months; range, three months to 24 months).
SD = Standard deviation of mean.
SE = Standard error of mean.

luride or a combination of these agents failed to elicit an increase in either electrolyte or water excretion. In these acute experiments, no immediate alterations were detected in the blood urea nitrogen, serum uric acid concentration or uric acid clearance. It was of extreme interest that uric acid clearance began to decrease after the fifth or sixth experimental period, a fact well documented in our chronic studies.[11]

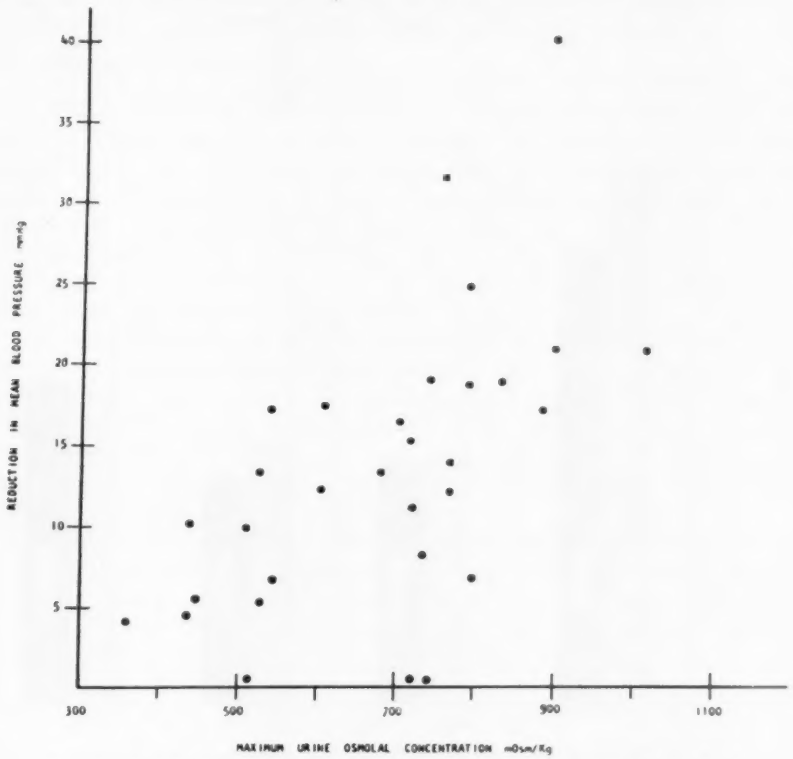

FIG. 2. Correlation of reduction in mean blood pressure* with the maximal urine osmolal concentration.

Long-Term Effects. The effects of long-term oral administration of thiazide diuretics to a group of 32 hypertensive patients with renal impairment are demonstrated in figures 2 and 3. The average reduction in mean blood pressure was 19 mm./Hg. No significant deterioration of renal function in these patients was detected as measured by blood urea nitrogen, maximal urine osmolal concentration, and glomerular filtration (creatinine clearance—figure 3, table 2). The maximal urine osmolal concentration in

* Mean blood pressure: diastolic + 1/3 (systolic-diastolic).

this group prior to therapy was 700 ± 14.0 * milliosmols/Kg. and 703 ± 12.9 * milliosmols/Kg. after an average of 6.6 months (range, three months to 24 months) of daily oral administration of 50 to 100 mg. of hydrochlorothiazide.† The pretreatment creatinine clearance was 69.1 ± 1.9 * ml./min. and 61.0 ± 3.1 ml./min. following prolonged administration. There was no significant change in the blood urea nitrogen (16.8 ± 1.3 * mg./100 c.c. prior to treatment, and 17.0 ± 1.5 * mg./100 c.c. at the end of the observation period).

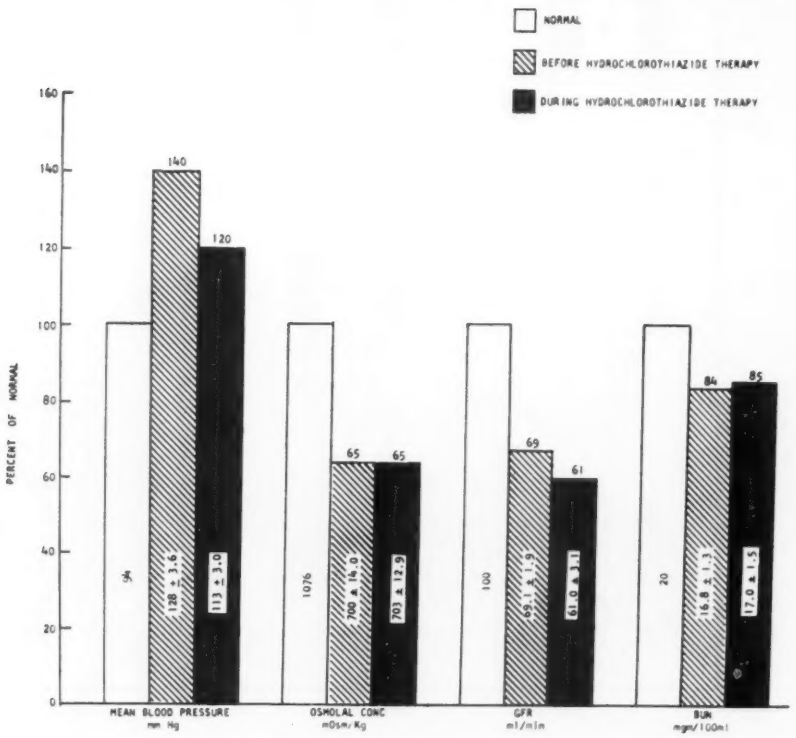

FIG. 3. Effects of long-term hydrochlorothiazide therapy on renal function in hypertensive patients.

COMMENT

The effects of intravenous hydrochlorothiazide on electrolyte and water excretion during isotonic diuresis in normal subjects and in the presence of moderate hypertensive renal disease were immediate. Urine flow, sodium,

*Standard error of the mean.

† In some patients, chlorothiazide, 1.0 gm. daily, was administered initially, and hydrochlorothiazide substituted when the latter became available for investigational use.

potassium, and total solute excretion increased within the first 10-minute experimental period. The glomerular filtration rate, renal plasma flow and filtered load of electrolytes were essentially unchanged, or tended to be reduced in the first or second period following the administration of hydrochlorothiazide. An abbreviated and diminished response was seen in the group of patients with moderate renal disease. Intravenous hydrochlorothiazide was not effective in eliciting either an electrolyte or a water diuresis in the patients with advanced renal disease (glomerular filtration rate, < 40 ml./min.).

The free water clearance was quite variable, but tended to decrease when a hypotonic urine was elaborated prior to intravenous hydrochlorothiazide therapy. Heinemann et al.[9, 10] found the free water clearance to decrease in eight, increase in seven, and remain constant in three of their combined group of 21 experiments in normal human subjects. Although hydrochlorothiazide may very well act to inhibit electrolyte reabsorption in both the proximal and the distal tubules, the tonicity and electrolyte content of the plasma and hydrating fluid undoubtedly influence the distal tubule as to water and electrolyte reabsorption.[8]

Long-term administration of hydrochlorothiazide was generally effective as a hypotensive and diuretic agent without engendering further renal impairment. It was interesting to note that a close correlation existed between the ability of the kidney to concentrate and the response in blood pressure reduction. This finding is not unexpected when compared to the water and electrolyte response in the normal subject as opposed to that seen in patients with advanced renal disease.

Blood pressure response in the hypertensive patient is undoubtedly attained without alteration of serum solutes, blood volume * or renal function. The actual mechanism by which thiazide diuretics cause a reduction in blood pressure may be similar to the inhibition of transport or secretory mechanisms for sodium, potassium and uric acid [11] at the renal tubular level.

Summary

1. Thiazide diuretics appear to reduce blood pressure and to diminish edema in the presence of minimal or moderately advanced renal impairment.

2. Hydrochlorothiazide was completely ineffective, either as a diuretic or as a hypotensive agent, in patients with advanced renal disease.

3. There was no consistent decrease in glomerular filtration or renal plasma flow in these acute experiments.

4. The water and electrolyte diuresis following thiazide injection appeared to be related to the remaining metabolic function of the kidney.

* Hypotension has been seen in patients depleted of sodium from large doses of thiazide medication, or in the presence of cirrhosis [14] or in chronic sodium loss in the presence of chronic glomerular nephritis.[15] However, this problem is familiar in many low-sodium syndromes, and may very well represent a marked loss of total body sodium.

5. A variable response in free water clearance was seen in these experiments, but was in part related to the electrolyte content of the hydrating fluid.

6. Prolonged administration of hydrochlorothiazide to hypertensive patients with varying degrees of renal impairment was safe and did not cause further deterioration of blood urea nitrogen, glomerular filtration or the maximal urine osmolal concentration.

SUMMARIO IN INTERLINGUA

Esseva effectuate 17 studios in 15 patientes: sex subjectos normal, septe patientes con moderatemente avantiate morbo renal hypertensive (filtration glomerular, 40 a 70 ml per minuta), e duo patientes con sever vitiation renal (filtration glomerular, minus que 40 ml per minuta). Post periodos de controlo de 10 minutas cata un, 0,5 g de chlorothiazida o 50 mg de hydrochlorothiazida o 2 ml de merallurida esseva injicite per via intravenose. Esseva determinate le filtration glomerular, le fluxo de plasma renal, le natrium del sero e del urina, e etiam le kalium, le solutos total, le clearance de aqua libere, e le acido uric.

In le subjectos normal e in patientes con non plus que moderatemente avantiate vitiation renal, le injection intravenose de diureticos thiazidic evocava un augmento immediate e persistente del clearance osmolar, del fluxo de urina, del excretion de natrium, de kalium, e del solutos total. Tamen, le patientes con moderatemente avantiate vitiation renal manifestava un abbreviate diurese, con relativemente minus marcate augmentos del excretion de electrolytos e de solutos total. Iste augmentos occurreva in despecto del facto que un tendentia reductori esseva manifeste in le valores pro le fluxo de plasma renal, pro le filtration glomerular, e pro le filtrate carga de natrium e de solutos total. Le clearance de aqua libere esseva satis variabile post merallurida e etiam thiazida, sed illo pareva depender del concentration de soluto in le solution de carga. In le presentia de un avantiate vitiation renal (filtration glomerular de minus que 40 ml per minuta), le administration intravenose de hydrochlorothiazida, de merallurida, o de un combination del duo evocava nulle augmento in le excretion de electrolytos e nulle in le excretion de aqua.

Esseva constatate nulle evidentia de deterioration del function renal in un gruppo de 32 patientes hypertensive con vitiation renal qui esseva tractate con diureticos a thiazida durante periodos de inter tres e 24 menses. Le maximo del concentration osmolal del urina e le maximo del clearance de creatinina ante le therapia esseva, respectivemente, 700 ± 14,0 milliosmols per kg e 69,1 ± 1,9 ml per minuta. Post un duration medie de 6,6 menses de therapia, le concentration osmolal del urina e le clearance de creatinina esseva inalterate (i.e. 703 ± 12,9 milliosmols per kg, respectivemente 61,0 ± 3,1 ml per minuta). Le nitrogeno de urea sanguinee e le creatinina del sero remaneva intra limites normal.

Esseva concludite que tanto le reduction del tension de sanguine como etiam le responsa electrolytic e diuretic al agentes thiazidic dependeva in parte del grado del remanente function renal.

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ISLET-CELL TUMORS AND PEPTIC ULCERS: CASE REPORT OF THE ZOLLINGER-ELLISON SYNDROME *

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Pancreatic endocrine function has long been suspect in gastroduodenal ulceration, although it has never been definitely and conclusively incriminated. The existence of an intrinsic factor of the pancreas that is not related to its external secretions but that may be active in peptic ulcerogenesis was postulated by Poth in 1948.[1] This concept was based on the earlier experimental observations of Dragstedt, Elman, Poth, and others that duodenal ulcers may be produced by deviation of the alkaline secretions of the pancreas by external fistulas or by ligation of the pancreatic ducts. These ulcers had usually been considered to be the result merely of depriving the duodenum of of the neutralizing influence of bile and of the pancreatic secretions on the acid effluent from the stomach.[2] It had also been observed, however, that if the duodenum is deprived of alkaline secretions by pancreatectomy, duodenal ulceration rarely supervenes. Dragstedt reported the incidence of experimental peptic ulcers following external pancreatic fistulas as almost 100%, and following pancreatectomy as 1.3%.[3] It appeared from these experiments that ulcer formation may not be adequately explained by failure of neutralization in the duodenum of the acid effluent, since the alkaline secretions had been lost in either instance.

The communication of Zollinger and Ellison in 1955, describing two cases of benign primary jejunal ulcerations associated with non-beta cell tumors of the pancreas, tended to confirm the suspected pancreatic influence on gastric secretion.[4] In 1956 Ellison published a review of 24 cases collected from various sources.[5] These, together with documented and tabulated, but not yet published, cases from various institutions, have brought to a total of 82 the cases known to have had an "ulcerogenic" pancreatic tumor. These tumors are composed of non-beta cells, with no clinical or laboratory evidence of insulin production in the majority of instances. Six of the 82 cases have shown some evidence of insulin production.[6]

Although the probability of a pancreatic non-beta islet-cell tumor's causing a severe fulminating ulcer diathesis appears to stand on firm clinical ground, there is not as yet convincing evidence of the mechanism involved, or of which of the non-beta cells predominates. The association of pancreatic islet-cell tumors and peptic ulceration must be considered to be more

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than a casual one, since in a few documented cases ablation of the islet-cell tumors resulted in a clinical subsidence of ulcer symptomatology when intensive medical treatment and radical gastric resection had failed to do so.[5, 6, 7] The mechanism by which the ulcerogenic tumors of the pancreas stimulate the gastric secretory cells remains a mystery; however, a direct peripheral or hormonal and, in turn, a chemical stimulation of the fundic glands appears to be the most plausible explanation. The known antral and cephalic phases of gastric secretion are not required in this syndrome. The removal of both of these phases of gastric secretion by radical subtotal gastrectomy and vagotomy, both above and below the diaphragm, uniformly fails to decrease gastric hypersecretion as long as any gastric mucosa remains under the influence of functioning ulcerogenic tumor tissue.

Studies of clinical cases of ulcerogenic tumors of the pancreas have resulted in the characterization of a diagnostic triad upon which nine of the more recent cases have been diagnosed preoperatively:

1. Gastric hypersecretion and hyperacidity. These are quite characteristic, with 12-hour nocturnal volumes of 2 to 3 L. in the absence of any pyloric obstruction. Hyperacidity appears to be uniformly present, and quantities as high as 300 mEq. of free hydrochloric acid have been observed, as compared to the normal of 18. It would appear that a 12-hour nocturnal gastric analysis is the best screening test whenever an ulcerogenic pancreatic tumor is clinically suspected.

2. Severe, recurrent, and often atypically located ulcerations. The ulcers may be multiple, and the fulminating ulcer diathesis persists despite the most intensive medical treatment or conventional radical surgical procedures which amount to anything less than a total gastrectomy. The usual definitive surgical measures of vagotomy, below and above the diaphragm, and radical subtotal gastric resection, have been uniformly unsuccessful as long as any gastric mucosa remained in the presence of functioning islet-cell tumor. These ulcerations are frequently atypically located, involving particularly the jejunum and distal duodenum, and they often recur soon after partial gastric resection and gastrojejunal anastomosis. The recurrence of a marginal ulcer within a few weeks after an acceptable ulcer operation is quite characteristic of this entity. Attempts at gastric irradiation have yielded only transient beneficial results.

3. The indentification of a non-beta cell adenoma of the pancreas by means of an exploratory laparotomy. This completes the clinical triad, and fulfills the criteria for the clinical entity now known as the Zollinger-Ellison syndrome.

The histologic definition of the offending pancreatic ulcerogenic tumors is still a debated and unsettled question. That the beta cells are not implicated appears certain, as the cellular elements are devoid of beta granules (figure 1), and hypoglycemia is not a characteristic feature in these patients. This is in contrast to Whipple's diagnostic triad of an insulin-producing

adenoma in which symptoms are due to hypoglycemia resulting from insulin overproduction, and are relieved by the administration of glucose. That the beta cells are not implicated in the ulcerogenic type of pancreatic adenomata would appear to be supported by the absence of peptic ulcerations in patients with known pancreatic beta-cell tumors resulting in prolonged and severe hypoglycemia, even to the point of unconsciousness and convulsions. With the exception of a single recorded instance,[8] peptic ulcers have not been found under these conditions. Poth and Fromm have reported a 50% incidence of peptic ulceration in dogs undergoing sustained insulin-induced hypoglycemia.[9] The explanation for the paradoxic lack of ulceration due to hypoglycemia in man is not apparent.

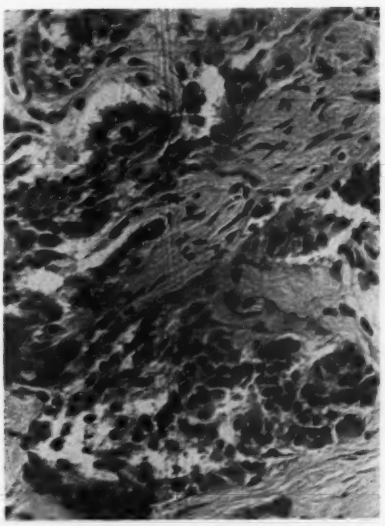

FIG. 1. High power photomicrograph showing cellular detail of islet-cell tumor devoid of beta granules. H & E; 420 ×.

Whether the ulcerogenic tumors arise from the alpha, delta, or gamma cells is still an unsettled issue, and all of the non-beta cells of the pancreatic islet must remain under suspicion until the villain is identified with a reasonable degree of certainty by histopathologic, clinical, or chemical means. These tumors have been variously called "non-insulin producing tumors" or "non-beta cell tumors," and the studies of the cellular nature of the tumors in the different reported cases are of little help, as they agree only in that the cells are not of the beta type.

That the ulcerogenic pancreatic tumors produce some powerful hormone with a profound influence upon the fundic glands appears to be inescapable. Failure in these patients to control the gastric hypersecretion by complete vagotomy and radical gastric resection points toward a peripheral and, in

turn, a chemical or hormonal stimulation of the gastric glands, since both the cephalic and antral phases of gastric secretion have been eliminated. That this as yet unidentified material is of pancreatic islet-cell origin is strongly suggested by the reported instances of decreased gastric secretion and subsidence of ulcer symptoms following ablation of the pancreatic tumors. A striking example has been reported by Oberhelman et al., in which a total pancreatectomy with removal of noninsulin-producing islet-cell carcinoma without further gastric resection or vagotomy resulted in a return to the normal in gastric secretion, with healing of a marginal ulcer and closure of a gastrojejunocolic fistula. The clinical remission observed by Oberhelman following total pancreatectomy, as well as other reported observations, lends strong circumstantial evidence that the ulcerogenic factor is of pancreatic islet-cell origin.[7]

The chemical nature of the ulcerogenic factor is one of the most controversial aspects of the Zollinger-Ellison syndrome. Because the islet-cell tumors suggestively appear to be of alpha-cell origin, and because the alpha cells are believed to secrete the hyperglycemic-glycogenolytic factor (glucagon), the original communication of Zollinger and Ellison suggested that glucagon may be the active ulcerogenic factor in overproduction. Since 1955, glucagon has undergone extensive experimental study, and there has been no reported evidence of any secretory-stimulating effect on the stomach either in voluntary human subjects or in Heidenhain-pouch dogs. Evidence at the present time indicates that the only physiologic property of glucagon is stimulation of hepatic glycogenolysis by stimulation of the phosphorylase system. Experimental work of Sutherland and Cori [10] has shown that when glucagon is added to liver slices, glucose is liberated more rapidly than in a control preparation. Although glucagon has not been experimentally convicted in peptic ulcerogenesis, it has yet to be excluded. Contrary to all reported experimental observations, Poth has observed a gastric secretory-stimulating effect of glucagon.[11] It seems conceivable that glucagon in vivo possesses some active principle which is not otherwise present, or has become inactive in the commercial preparations. Little is actually known about the function of the non-beta cells of the pancreatic islets. Whether the alpha, delta, or gamma cells produce other endocrine substances remains unknown. From the lack of information concerning the physiologic function of the non-beta cells of the pancreatic islets, it follows that no biochemical test is available to detect the presence of an ulcerogenic pancreatic tumor.

There is at least some suggestive evidence that the activity of the mysterious ulcerogenic factor may be preserved under conditions of freezing. By preparing extracts of frozen ulcerogenic tumor tissue, Osborne [12] has observed a transient gastric secretory stimulation as well as a transient lowering of the pH in Heidenhain pouches following intravenous administration of the prepared extract. It is not definitely clear whether the gastric-stimulating effect was due to some preserved active principle in the tissue, or

to the histamine normally present in living tissue. At any rate, whenever such a rare tumor is identified and resected, it should be frozen quickly under sterile conditions. In this way its active principle may possibly be preserved, to be extracted later and perhaps eventually to be identified.

Morphologically, the typical ulcerogenic adenoma consists of one or more nodules composed of clusters and cords of uniform cuboidal to cylindric cells, surrounded by densely proliferating fibrous connective tissue. The cells are characterized by oval nuclei with one to several nucleoli, a finely dispersed chromatin network, and a finely granular cytoplasm, frequently with some vacuolization, but no evidence of secretory granules. These tumors of the pancreatic islets have practically the same microscopic appearance as carcinoid tumors. It has been previously suggested that the pancreatic islet-cell tumors may be metastatic carcinoids. Elevated serum and urinary serotonin, which occur with carcinoid tumors, have not been observed in patients with ulcerogenic pancreatic tumors.

Zollinger and McPherson [13] have recently reported a case of gastric hypersecretion and fulminating ulcer diathesis characteristic of the ulcerogenic pancreatic tumor. No pancreatic tumor could be identified at the time of operation; however, the body and tail of the pancreas were resected because of the strong clinical suggestion of the ulcerogenic tumor triad. Microscopic examination of the resected pancreatic tissue revealed not only an increased number of islets but also a greater proportion of non-beta to beta cells. A similar observation has been reported by Summerskill.[14] In both cases the hyperplastic elements appeared to be alpha cells; and in the latter case the post-coupled benzylidene reaction, which demonstrates the tryptophan component of glucagon, suggested increased alpha-cell activity which was compatible with a patchy alpha-cell hyperplasia. Such a condition is stated by Zollinger to be analogous to hyperplasia of the parathyroid glands, resulting in a clinical picture identical with that of a parathyroid adenoma.[15] It appears that the clinical manifestations produced by islet-cell hyperplasia should be identical or very closely similar to those resulting from an islet-cell adenoma, as long as the non-beta cell adenomata continue to be considered hormone-producing structures. At least this appears to be the case among other endocrine organs of the body, particularly the adrenal cortex, the thyroid, and the parathyroids. If hyperplasia of the non-beta islet cells likewise proves to be ulcerogenic, then an overproduction of some hormone is again suggested. A pancreatic role in gastric secretion has been long suspected but never conclusively proved. The association of gastric hypersecretion with islet-cell adenomata or islet-cell hyperplasia again lends circumstantial evidence that normal pancreatic islets exert some endocrine influence on gastric secretion. If such a hormone could be identified, then the practical implications would be immense, not only in the rare ulcerogenic adenoma patient, but also in the baffling and much too common syndrome of gastroduodenal ulceration.

Diarrhea has been reported as an early and prominent feature in seven documented cases of the Zollinger-Ellison syndrome. Improvement in diarrhea following alleviation of the gastric hypersecretion has been reported in three cases.[14, 16, 17] The mechanism of this diarrhea is obscure, but the evidence presented in the three reported cases points to a direct association with gastric hypersecretion. It is possible that the acid and pepsin are irritating to the small intestine, giving rise to a hypermotility of the small intestine. Preoperative intubation of the small intestine by Summerskill showed a low pH (1.3 to 1.4) in the lower duodenum and upper jejunum, where the normal pH usually ranges between 5.0 and 8.0. Diffuse mucosal damage in the upper intestine was found by Summerskill on aspiration biopsy, later confirmed on the surgical specimen. The abnormal acid-pepsin concentration in the upper intestine for much of the 24 hours of the day could well account for the frequency of lower duodenal and upper jejunal ulcerations found in these patients.

Steatorrhea has been a reported feature in only one of the seven cases of Zollinger-Ellison syndrome exhibiting a severe diarrhea. Pancreatic lipase is the most significant enzyme in fat absorption, with an optimal pH of 7.0. Depressed lipase activity in the acid milieu of the upper small intestine appears to be a feasible explanation. Fat absorption begins in the duodenum, and is completed within the proximal 100 cm. of the jejunum corresponding quite closely to the portion of the upper small intestine in which Summerskill was able to demonstrate a remarkable depression of the pH.[14]

At the present time, the diagnosis of an ulcerogenic pancreatic tumor can be definitely established only by surgical exploration. Nevertheless, there are certain clinical features and preoperative findings which should focus attention on the pancreas. One third of the ulcers in these patients have been unusual in their location, e.g., the postbulbar duodenum, jejunum, and esophagus. The presence of a primary nonspecific ulceration of the jejunum appears to be almost pathognomonic of an ulcerogenic pancreatic tumor. It is of particular interest that the previously reported jejunal ulcers were particularly noted for a high recurrence rate and a high mortality rate.[18, 19] Because insufficient attention was paid to the pancreas in these patients, conclusions regarding the presence or absence of ulcerogenic pancreatic tumors cannot be made; however, evidence at present would seem to suggest that these patients were harboring islet-cell tumors. Any patient with a severe ulcer diathesis not amenable to intensive medical therapy in whom stomal ulceration develops following partial gastrectomy, with or without vagotomy, should raise suspicion of the possibility of a noninsulin-producing islet-cell tumor. The finding of high volumes of gastric juice on a 12-hour nocturnal gastric aspiration in the absence of pyloric obstruction should be viewed with suspicion, especially if the acid concentration is high. It appears that the finding of more than 100 mEq. of free hydro-

chloric acid on a 12-hour overnight aspiration should likewise suggest the strong possibility of a non-beta cell adenoma. The finding of other endocrine abnormalities in the ulcer patient should suggest the possible involvement of the pancreas as well. Roentgenologic evidence of hypertrophic gastritis or duodenal ileus, with or without polypoid changes in the duodenal wall, may be helpful, as these findings have been described in this group of patients.

Pluriglandular adenomatosis has been present in 17 of the 82 known cases with other functioning endocrine tumors as well as the pancreatic adenomata. The endocrine systems involved, in a decreasing order of frequency, are: (1) adrenal cortex, (2) pituitary adenoma, (3) pancreatic beta-cell insulinoma, and (4) parathyroid adenoma.

The ulcerogenic tumor can usually be detected on gross examination of the pancreas as a firm, discrete mass, occurring in the body and tail of the pancreas about two thirds of the time. About 10% of these tumors are found in aberrant locations, such as the splenic hilus, within the gastric and duodenal walls, suprapancreatic region, or in any location where heterotopic pancreatic tissue can occur, and they have been a feature in nine of the 82 documented cases. Oberhelman has observed six cases where the tumors have been found within the duodenal wall without concomitant tumors within the pancreas proper; however, in all of these cases he did observe a concomitant islet-cell hyperplasia.[20] Diffuse involvement of all of the islets has occurred in about 10% of the cases that could be detected only on microscopic examination. The pancreas should be carefully examined at every operation for an intractable ulcer or its complications, especially if the ulcer has recurred after the acceptable definitive surgical measures have been performed. Even if no pancreatic tumor is grossly detected, but there is sufficient reason to suspect an ulcerogenic tumor on a clinical basis, resection of the body and tail of the pancreas is justified for histologic diagnosis, since this is where the majority of the offending tumors appear to be situated. In addition, a hemipancreatectomy will allow recognition of islet-cell hyperplasia which would otherwise escape detection. In about one third of the cases the tumors located in the pancreas have been multiple, and approximately 15% of these could not be detected by palpation. Microscopic features of malignancy have been demonstrated in two thirds of these cases, and approximately one third of these had spread beyond the confines of the pancreas when first identified, with the liver being the most frequent site of metastasis, followed by the peripancreatic lymph nodes. About one-half of the metastases have been found to function regardless of their size, and the ulcer diathesis continued to be a dilemma in their presence. The degree of cellular differentiation must determine whether a metastasis will continue to function, but there are as yet no known microscopic features which allow a distinction to be made between functioning and nonfunctioning metastases. The growth and metastatic spread of these tumors appear to be extremely

slow; therefore, resection of the primary tumor may still be of benefit, even when gross metastases are detectable.

The common denominator of all of the foregoing statements is that the fulminating ulcer diathesis could be alleviated by removal of all of the functioning ulcerogenic tumor tissue. In view of the multiplicity of tumors, the extremely high incidence of malignancy, the possible presence of tiny, undetectable metastases, and the statistically strong possibility of diffuse pancreatic-islet involvement, definitive removal by the surgeon of all functioning tumor tissue can be considered to be a nearly hopeless expectation. For this reason, any surgical procedure consisting of anything less than a total gastrectomy is almost certainly doomed to failure. All of the complications of an ulcer with high mortality are commonplace in this group of patients with fulminating ulcer diathesis. The conclusion to be drawn from all of these statements is that the surgical identification of an ulcerogenic pancreatic tumor should be accompanied by a total gastrectomy. The following case report demonstrates this principle.

Case Report

A 34 year old Negro female was first seen in the Out-patient Department of the University of Texas Hospitals on March 1, 1955, with the chief complaints of vomiting and presternal chest pain radiating along the left costal margin. History revealed that she had been having upper abdominal distress for one year. Physical examination revealed epigastric tenderness with muscle guarding on palpation, but was otherwise not remarkable. One year previously an abrupt cessation of menses had occurred for which no clinical explanation could be given. The present symptoms were somewhat suggestive of a peptic ulcer, and the first upper gastrointestinal series (March 3, 1955) revealed clearly the presence of *two* active duodenal ulcers (figure 2). The Sippy ulcer regimen with anticholinergics was instituted.

The patient continued to be seen in the Out-patient Clinic until June 1, 1955. During this time there was some improvement of symptoms; however, early morning awakening, coupled with characteristic peptic ulcer pain, seemed to be persistent. In the early part of June, 1955, the patient moved to another section of Texas and was not seen again until November 25, 1955, when she appeared in the University Hospitals' Emergency Room with complaints of vomiting and substernal chest pain radiating to the back and left costal margin. Interim history indicated that she had remained virtually asymptomatic on a modified medical ulcer regimen until October, 1955, when intermittent episodes of epigastric distress recurred. A strict medical ulcer regimen was again instituted. An active duodenal ulcer, with evidence of pylorospasm, was demonstrated on a repeated upper gastrointestinal roentgenogram on November 30, 1955. The patient was followed at frequent intervals in the Out-patient Clinic for the following year—November, 1955, to November, 1956. During this time there was symptomatic improvement, interrupted by episodic bouts of active ulcer symptoms. Radiographic examination of the upper gastrointestinal tract on October 25, 1956, clearly demonstrated an active duodenal ulcer with a crater, despite what was believed to be a reasonable adherence to a medical ulcer regimen. On November 28, 1956, the patient returned to the Out-patient Clinic with vomiting and severe upper abdominal pain, and was admitted to the University of Texas Hospitals for the first time.

On admission to the hospital, there was no evidence of hematemesis, nor was any

history of hematemesis elicited. The epigastric pain was described as quite severe, with penetration to the back and right scapular region. Except for localized epigastric tenderness, the physical examination was nonrevealing. A perforating duodenal ulcer with early pancreatitis was clinically suspected; however, the serum amylase level was found to be only 90 Somogyi units. Because of the possibility of a perforating duodenal ulcer, a continuous Wangensteen suction was instituted, and an overnight volume of 1,250 c.c. of gastric juice was recovered. Titration results of a fasting gastric aspirate were: total acid, 50 degrees; free acid, 26 degrees. Fecal examinations for occult blood were negative. Roentgenologic examination confirmed an active duodenal ulcer. The patient's first hospital course was essentially uneventful, and she was discharged on December 8, 1956, on a bland diet, antacids, anticholinergics, and meprobamate. She was not seen again until May 17, 1957, when she appeared in the University Hospitals' Emergency Room with symptoms of an active peptic ulcer, which was confirmed roentgenologically. Symptomatic

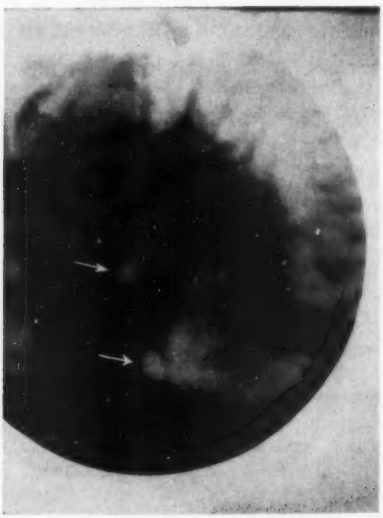

FIG. 2. Roentgenogram, March 3, 1955, showing two active duodenal ulcers.

relief was again obtained on a medical ulcer regimen. In September, 1957, because she was asymptomatic, the patient discontinued her medical ulcer program without medical supervision. In November, 1957, she noted a gradual, progressive return of peptic ulcer symptoms, resistant to the usual medical therapy.

On January 15, 1958, the patient was admitted to the University of Texas Hospitals for the second time because of active ulcer symptoms, with severe vomiting and pain penetrating to the interscapular region. Serum calcium and serum phosphorus were found to be 7.5 mEq./L. and 1.8 mEq./L., respectively. These findings were reproduced seven additional times. Urinary calcium determinations ranged from 131 to 370 mg. per 24 hours on a diet not exceeding 150 mg. calcium daily. Total serum proteins and serum alkaline phosphatase were within normal limits; osseous changes and nephrolithiasis were not radiographically evident. Hyperparathyroidism seemed quite likely, and surgical exploration of the parathyroid glands was deemed advisable. However, the patient refused any surgical procedure, and was discharged on February

19, 1958, only to be re-admitted on March 13, 1958, with an aggravation of ulcer symptoms. Biochemical studies were again compatible with hyperparathyroidism. It was then the opinion of all concerned that the etiology of this woman's intractable ulcer diathesis was now clearly defined. On April 28, 1958, surgical exploration of the neck resulted in identification and resection of two parathyroid adenomata. The postoperative course was uneventful, and she was discharged from the hospital five days postoperatively. However, interpretation was rendered difficult when symptoms of epigastric distress continued. She was again admitted to the University of Texas Hospitals on September 19, 1958, with severe ulcer symptoms and vomiting. An upper gastrointestinal roentgenogram confirmed an active duodenal ulcer, with no evidence of pyloric obstruction. Suspicion of Zollinger-Ellison syndrome arose. Residual hyperparathyroidism could not be confirmed by biochemical tests. A 12-hour nocturnal gastric aspiration resulted in a volume of 2,200 c.c., with 167.2 mEq. free acid and 187 mEq. total acid. On October 30, 1958, an exploratory laparotomy was carried out. Two pancreatic tumor masses were grossly identified and resected, and proved to be nonmalignant, non-beta cell adenomata. In addition, a 60% subtotal gastrectomy and Polya-type gastrojejunostomy were accomplished. Postoperatively the patient's course was considered to be satisfactory, and she was discharged on November 15, 1958.

Within three days following discharge, vomiting and epigastric distress, with occasional pain radiating to the back and interscapular region, were noted to be recurring. The patient returned to the Emergency Room of the University Hospitals on November 20, 1958. The possibility of obstruction at the gastrojejunal anastomosis was considered, and the patient was re-admitted to the hospital for observation. A six-day hospital course, with antacids and methscopolamine (Pamine), resulted in a subsidence of all symptoms.

For the ensuing three months, epigastric burning and intermittent nausea and vomiting continued. In December, 1958, urinary steroid quantitation was within normal limits, and no trace of follicle-stimulating hormone was found on bio-assay. Vomiting and severe upper abdominal pain resulted in admission to the University Hospitals on March 4, 1959, for diagnostic investigation. Stomal ulceration was suspected clinically. The examining radiologist suspected a marginal ulcer, but no definite radiographic proof could be obtained. A 12-hour nocturnal gastric aspiration resulted in a volume of approximately 850 c.c., with 30 mEq. free acid and 47.5 mEq. total acid. Rather surprisingly and unexpectedly, the administration of methscopolamine decreased the 12-hour volume to 202 c.c., with 3.02 mEq. free acid and 8.8 mEq. total acid. The validity of these determinations remained in question, because of the altered anatomy from the previous gastroenterostomy, and evident bile staining in some of the collected specimens. The rather remarkable drop in the gastric secretion following methscopolamine suggested that the acidity could probably be controlled by the use of vagal blocking agents. Repeated urinary steroid studies and thyroid function studies were within normal limits. Fecal examinations for occult blood were negative. Sedation and a medical ulcer regimen brought the symptoms under control, and the patient was discharged after a 12-day hospital course.

Soon after this discharge the patient noted a rapid recurrence of unrelenting upper abdominal pain and burning, despite antacid and anticholinergic therapy, and consulted private physicians elsewhere. In May, 1959, she required a blood transfusion in another hospital because of massive upper gastrointestinal hemorrhage. She was referred back to us on October 12, 1959, and was hospitalized in the University of Texas Hospitals on that date. An upper gastrointestinal radiographic examination revealed a gigantic anterior marginal ulcer, with two other suspicious areas of ulceration (figures 3 and 4). Repeated attempts at a nocturnal gastric

FIG. 3. Roentgenogram, October 13, 1959, showing a gigantic anterior marginal ulcer.

analysis met with failure because of thick, mucinous gastric secretions. Fecal examinations for occult blood were strongly positive, and a blood transfusion was required soon after admission. Urinary steroid measurements again yielded results within normal limits, and biochemical tests for hyperparathyroidism were not confirmatory. That this woman must have residual ulcerogenic tumor tissue appeared certain, and this was confirmed on surgical reëxploration on December 4, 1959.

FIG. 4. Roentgenogram showing the gigantic anterior marginal ulcer with a fluid level.

FIG. 5. Photograph showing the tumor mass in the tail of the pancreas.

At operation, the presence of a gigantic perforated marginal ulcer was confirmed. A 2.0 by 2.5 cm. tumor mass was identified in the distal end of the tail of the pancreas (figure 5); on resection, it was found to be an adenoma arising from a pancreatic islet. Several firm tumor masses could be palpated throughout the body and tail of the pancreas. The tail, body, and a portion of the head of the pancreas, as well as the spleen, were resected. No grossly palpable tumors could be detected in the

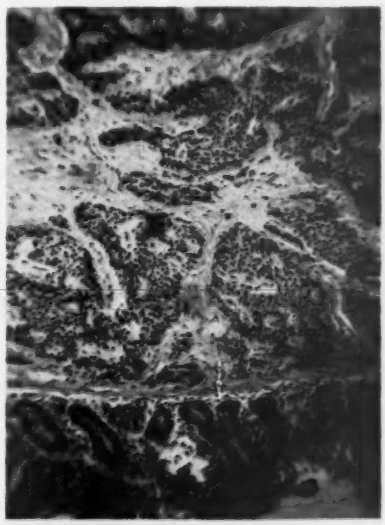

FIG. 6. Photomicrograph showing an aberrant islet-cell adenoma within the duodenal wall. 90 ×.

remaining portion of the head of the pancreas, which was not removed. Upon careful examination of the duodenal wall, three firm, submucosal nodules, each about 5 mm. in diameter, were found and resected. These proved to be aberrant islet-cell adenomata within the duodenal wall (figure 6). Two of these aberrant islet-cell adenomata were located along the lesser curvature of the duodenum near the orifice of the duct of Santorini; the third aberrant islet-cell adenoma was situated on the contralateral duodenal wall at approximately the same level. The identification of pancreatic islet-cell adenomata in this patient was accompanied by a total gastrectomy and construction of a jejunal pouch anastomosed to the esophagus.

The resected pancreatic tissue was found to be harboring at least 12 distinct islet-cell adenomata, some of which were microscopic in size and could not be detected grossly. No microscopic features of malignancy were evident; these adenomata throughout the substance of the pancreas were considered to be islet-cell neoplasms of multifocal origin. Individual microscopic examination of each of the neoplasms revealed the characteristic morphologic features of non-beta islet-cell tumors; Gomori's chromic hematoxylin stain confirmed the conspicuous absence of beta granules. (Pathologic description by Dr. John H. Childers.)

Discussion

Although the majority of these unfortunate patients have had but a single primary ulcer, multiple ulcers have been reported, and should call to the physician's mind the possibility of a pancreatic ulcerogenic tumor. The radiographic demonstration of two separate, distinct, active duodenal ulcers was strongly suggestive of this entity. The response to medical therapy at the onset of symptoms in the various reported cases has been inconsistent and somewhat variable. The interval of time from onset of symptoms until surgical intervention has varied from a few days to as long as 30 years, with the average time being nearly six years. Massive hemorrhage has constituted the most frequent indication for surgical intervention.

A rapid recurrence of ulceration following what is considered to be an adequate operation for the uncomplicated ulcer is the single most outstanding clinical feature of this entity. Irradiation of the gastric remnant and intensive medical therapy have been uniformly unsuccessful in preventing the secondary gastroduodenal or gastrojejunal ulcerations; and duodenocolic or gastrojejunocolic fistulas have been reported in several instances. Characteristically, within a few days of operation a severe, constant, unrelenting, boring type of upper abdominal pain occurs which may well be the prodrome of an impending perforation. Massive hemorrhage is the most common complication of the large penetrating ulcer which develops at a rapid pace in this group of individuals.

In the case cited above a surgical procedure short of total gastrectomy would almost certainly have been doomed to failure. In view of the pancreatic involvement with microscopic adenomata which escaped detection grossly, there is little reason to doubt that ulcerogenic tumor tissue remained behind in the unresected portion of the head of the pancreas. It is likewise possible that additional aberrant islet-cell adenomata within the duodenal

wall escaped detection. Also, it must be recognized that undetected aberrant islet-cell adenomata could have remained behind in any place where heterotopic pancreatic tissue can occur. The surgeon has no way of determining if all functioning tumor tissue has been removed except by measuring gastric secretion and acidity postoperatively. Death in these patients is not due to the neoplasm per se, but rather to all of the known complications of an ulcer, which are commonplace in this group of patients. Therefore, until the mysteries of this syndrome are solved, it appears that a total gastrectomy is the wiser course, despite the fact that both the patient and the physician are committed to a long program of rehabilitation.

Gastroduodenal ulceration is a known complication of hyperparathyroidism. It is of particular interest in the above case report that resection of the parathyroid adenomata failed to alleviate the gastric hypersecretion and fulminating ulcer diathesis. The relationship between the pancreatic islet-cell tumors and recurrent peptic ulceration must be considered to be more than a casual one; evidence appears to indicate that the pancreatic islet-cell tumors were the ultimate offenders in this patient.

Summary

Pancreatic endocrine influence on gastric secretion has long been suspected but never conclusively proved. The report by Zollinger and Ellison in 1955 of two cases of primary jejunal ulcerations and gastric hypersecretion associated with a non-beta cell adenoma of the pancreas tended to confirm the suspected pancreatic influence on gastric secretion. Although the association of islet-cell tumors and peptic ulcers appears to stand on firm clinical ground, the mechanism by which these tumors stimulate the fundic glands remains a mystery; however, a direct hormonal stimulation is suspected. The identification of such a hormone would be of immense value, not only in the rare ulcerogenic pancreatic adenoma patient, but also in the much too common syndrome of gastroduodenal ulceration.

The diagnostic ulcerogenic tumor triad, as characterized by Zollinger and Ellison, appears to be standing the test of time; we may expect more of these patients to be recognized in the future. A total gastrectomy in the peptic ulcer patient harboring islet-cell tumors appears to be the wiser course of action until the mechanism of this syndrome is elucidated. A case demonstrating this principle is reported.

Addendum

The patient in the Case Report is enjoying good health subjectively and objectively eleven months postoperatively. Since the time of the total gastrectomy on December 4, 1959, this patient has shown a weight gain of 15 pounds. Therapy has consisted of pancreatic enzyme replacement in addition to parenteral vitamin B_{12} for prevention of pernicious anemia.

Acknowledgments

The author is much indebted to Dr. Edgar J. Poth for his many constructive suggestions and profitable contributions during the study of the reported patient. Appreciation is also

expressed to Dr. John E. Johnson, Jr., for his suggestions during the preparation of this manuscript and his proofreading of the completed work.

SUMMARIO IN INTERLINGUA

In 1955, Zollinger e Ellison reportava duo casos de benigne primari ulceres jejunal, associate con tumores de cellulas non-beta del pancreas e alte nivellos de aciditate gastric resistente al tractamento chirurgic conventional. Ille communication tendeva a confirmar le longemente suspicite sed non ancora provate influentia del pancreas super le secretion gastric e forniva supporto additional pro le theoria del existentia de un factor intrinsec del pancreas que esseva postulate per Poth in 1948.

Depost 1956, 82 casos ha essite reportate in que le relation causal inter tumores a cellulas insular e un diathese pro fulminante ulcere peptic es apparentemente basate super un firme fundo clinic. Le mechanismo del stimulation del glandulas gastric non es cognoscite. Tamen, un directe stimulation chimic per le un o le altere hormon de origine in le cellulas insular del pancreas es suspicite in consideration del facto que le phases antral e cephalic del secretion gastric non es indispensabile in iste syndrome. Si un tal hormon poteva esser identificate, le consequentias practic pro le multo troppo frequente syndrome de ulceration gastroduodenal esserea immense.

Le diagnose de un tumor pancreatic a potentia ulcerogene es establibile solmente per exploration chirurgic, sed il existe certe characteristicas clinic e certe constatationes pre-operatori que pote diriger le attention verso le pancreas. Istos es (1) hypersecretion e hyperaciditate gastric e (2) sever, recurrente, frequentemente multiple, e frequentemente atypicamente locate ulceres. Le rapide recurrentia de ulceration post un adequate tractamento chirurgic de non complicate ulceres es le plus eminente characteristica clinic.

Morte resultante de complicationes de ulcere peptic plus tosto que del neoplasma per se es un evento commun in iste gruppo de patientes. Le frequente presentia de un multiplicitate de tumores, le extrememente alte incidentia de malignitate con distante metastases, e le non infrequente location de tissu tumoric a cellulas insular in sitos aberrante rende le ablation chirurgic de omne le ulcerogene tissu tumoric practicamente impossibile. Pro iste ration, le identification chirurgic de un tumor de cellulas insular non-beta in un patiente con ulceres peptic deberea esser considerate como un indication pro gastrectomia total. Il pare que isto es le sol via de sagessa e va remaner lo usque le mysterio de iste syndrome es plus plenmente elucidate.

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THERAPY WITH AMPHOTERICIN B IN NORTH AMERICAN BLASTOMYCOSIS *

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The therapy of North American blastomycosis has not been completely satisfactory in the past. Although the aromatic diamidines, particularly stilbamidine and the less toxic 2-hydroxystilbamidine, have proved to be effective and distinctly more potent than potassium iodide, x-ray, or vaccine therapy, significant numbers of patients have been resistant to therapy, or have experienced recurrences of the disease despite large amounts of the diamidines given over long periods.[7, 13] Recent trials of amphotericin B [2, 6, 7, 10, 11, 14] have shown that it is an effective therapeutic agent for a variety of deep mycotic infections, including North American blastomycosis. Indeed, in several reports, amphotericin B is considered to be the treatment of choice for this infection. The number of patients treated, however, is limited, and reports of only 26 patients so treated could be found.[1, 2, 3, 5, 7, 10, 11, 13, 14] The response was considered to be good in all but two individuals. To augment this experience, this report will summarize the results of therapy with amphotericin B † in 17 patients with *Blastomyces dermatitidis* infections. Since there are excellent recent reviews of both North American blastomycosis [4] and the properties of amphotericin B,[2, 6, 9] these general aspects will not be discussed.

Patients

The significant features of the individual patients are summarized in table 1. The duration of disease prior to therapy with amphotericin B ranged from three months to 10 years, with an average of 27 months. A majority of patients had disseminated disease with multiple system involvement; however, two patients had only cutaneous lesions, and five had pulmonary disease only. Most of the patients (10 of the 16 tested) gave negative skin reactions and positive serologic reactions ‡ to blastomyces antigens, an immunologic response found by Smith to be associated with a poor prognosis and often death at a time when no adequate therapy was available.[12]

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† Much of the amphotericin B was supplied as Fungizone by John T. Groel, M.D., Squibb Institute for Medical Research, New Brunswick, New Jersey.

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‡ Precipitin reactions were kindly done by D. C. Heiner, M.D., Department of Pediatrics, using his technic of double diffusion in agar.[8]

TABLE 1

Results of Amphotericin B Therapy in North American Blastomycosis

Case Information						Immunology			Amphotericin B Therapy			
						Serology						
Patient	Age	Race	Sex	Duration of Disease	System Involvement	Skin Test	Comp. Fix.	Precipitin	Duration	Total Amt. mg.	Results	Follow-up after Therapy (months)
M.A.	52	N	F	2 years	Lungs, bones	0	1:8	0	25 days	680	Healed	25
F.B.	56	W	M	18 mos.	Skin, oropharynx	0	1:16	0	30 days	1,130	Prompt healing; recurrence 3 mos.	
									2 weeks	500	Prompt healing	23
W.B.	24	N	M	8 mos.	Skin, lungs	0	1:16		19 days	1,170	Healed	19
J.B.	26	W	M	2 years	Lungs	+	0	0	12 weeks	3,125	X-ray clearing; sputum negative	10
J.C.	61	W	M	8 mos.	Lungs	0	1:16	0	7 weeks	2,160	Healed	18
F.C.	49	W	M	10 years	Skin, lung, joints	0	1:8	+	5 weeks	1,390	Prompt clearing; recurrence 15 mos.	
									4 weeks	500	Skin improved; refused further therapy	1
H.D.	49	N	F	1 year	Skin, lungs	0		0	6 weeks	1,950	Prompt clearing	1
J.G.	64	W	M	1 year	Skin	0	0		3 weeks	1,000	Healed	6
R.G.	30	N	F	3 years	Skin, lungs, bones	0	1:64	+	12 days	300	Prompt healing	13
J.H.	79	W	M	?4 years	Skin, ?lungs		1:32		6 weeks	930	Prompt healing; died of prostatic bleeding	½
P.H.	50	W	M	?2 years	Disseminated	0	0	+	13 days	640	Died	
D.L.	14	N	F	3 mos.	Bone, skin	0	0	0	7 weeks	2,010	Healing	6
E.L.	64	W	M	?8 years	Lungs	0	1:8	0	8 weeks	2,035	Sputum cleared; x-ray unchanged	6
J.L.	56	W	M	2 years	Skin, ?lungs	+	0		1 day	10	No further therapy attempted	
W.M.	62	W	M	6 mos.	Skin	0	0	0	4 weeks	1,500	Healed	18
M.M.	52	N	M	4 mos.	Lungs	0	0	+	5 weeks	1,850	Healed	18
A.T.	24	W	M	3 years	Lungs	0	1:16	0	8 weeks	1,900	No change; killed in accident	2

Ten patients had received no previous therapy, while seven had been treated with an aromatic diamidine. In three (F. B., W. B., J. L.), 2-hydroxystilbamidine had been given orally for from two to three months. W. B. showed clearing of cutaneous lesions but persistence of pulmonary disease, while the other patients had persistent disease. The other four individuals had received either stilbamidine or 2-hydroxystilbamidine intravenously. Only A. T. had had an adequate amount of therapy, while patients F. C., W. M., and R. G. had received courses of 1.5 gm., 2 gm. and 4.7 gm., respectively. In all four, disease persisted despite the diamidine therapy. Patient F. C. had also received several courses of potassium iodide and local x-ray for recurrent cutaneous lesions.

Amphotericin B Administration and Toxicity

One patient (J. L.) received 150 gm. of amphotericin B orally over 10 weeks with questionable benefits, and later was given one injection intravenously. All other patients were given amphotericin B intravenously. It was usually administered in daily injections, starting with an initial dose of 0.25 mg. per kilogram of body weight, and increasing to a maximal daily dose of 1 mg. per kilogram, as tolerated. The agent was infused in 500 or 1,000 ml. of 5% dextrose in distilled water over a six-hour period. To circumvent or reduce reactions, additional medications commonly given included salicylates, antihistamines, codeine, and various phenothiazine derivatives. The duration and total amount of therapy for each individual are recorded in table 1.

As pointed out by others, it is apparent that the necessary parenteral administration of this drug has several disadvantages. One is that hospitalization is required for one or two months to maintain an effective dosage schedule. In addition, toxic reactions are common; fortunately, these are ordinarily short-lived and not serious. The toxic reactions occurring in this series of patients are summarized in table 2. Fever, chills, nausea, vomiting, and headache were most common. General malaise and anorexia frequently occurred, but caused temporary interruption of therapy in only one individual. Thrombophlebitis was experienced by two patients, but was minor in both. In one patient, bromsulfalein retention rose from 2% before therapy to 17% during therapy, then fell to normal. No other evidence of hepatic dysfunction was encountered.

Most impressive were the nephrotoxic reactions to amphotericin B. Elevation of the blood urea nitrogen or blood nonprotein nitrogen occurred in 12 patients. In seven, therapy was interrupted, with a resultant decrease in the azotemia, usually within two to five days. In two individuals, therapy was stopped because of azotemia. One patient (J. L.) with diabetes mellitus and pyelonephritis experienced a rise in the blood urea nitrogen from 24 mg.% to 57 mg.% following a single 10 mg. injection of amphotericin B; no further therapy was attempted. After 1.85 gm. had been admin-

istered to another patient (M. M.), the blood urea nitrogen rose to 66 mg.% and remained abnormal for 10 days after stopping therapy; the urea clearance was also depressed (to 45%). In two additional patients (D. L., H. D.) depression of both urea clearance and phenolsulfonphthalein excretion was also noted at completion of therapy. One (H. D.) exhibited a profound hypokalemia after having received 2 gm. of amphotericin B. The serum potassium fell to 1.6 mEq./L., and the fall was associated with severe muscular weakness. Following parenteral and oral potassium therapy and discontinuance of amphotericin B, the serum potassium returned to normal within six days. The blood urea nitrogen, which had been 26 mg.%, also promptly fell (to 14 mg.%). A renal biopsy one week later showed no abnormalities. Transient cylindruria was seen in three patients, all of whom also had azotemia. No permanent renal damage was recognized in any patient, and the azotemia and cylindruria cleared in all individuals. However, detailed renal functional studies were not done routinely.

TABLE 2

Toxicity of Amphotericin B

Reaction	Number of Patients	Percentage of Total Patients
Fever, chills	13	76
Nausea, vomiting	11	65
Azotemia	12	71
Cylindruria	3	18
Thrombophlebitis	2	12
Anemia	2	12
Hypokalemia	1	6
Bromsulfalein retention	1	6

A significant fall in hemoglobin occurred during therapy in two patients (J. B. and D. L.) despite healing of their infections. Within two months after therapy had been completed, the hemoglobin rose to normal levels in both. The mechanism of this anemia is presently being investigated in other patients receiving amphotericin B.

RESULTS OF THERAPY

The individual responses to treatment are included in table 1. Of the 17 patients, 14 exhibited healing, with the onset of improvement usually by the second week. An example of the prompt response of cutaneous lesions is shown in figures 1 and 2. This patient (J. H.) experienced rapid healing, but two weeks after therapy he died from uncontrolled traumatic prostatic hemorrhage following self-removal of an inflated urethral catheter. Unfortunately, he was not seen by the authors during this episode, and no autopsy was obtained. Recurrence of the disease was seen in two of these 14 patients, one (F. B) at three months after therapy with 1.13 gm., and the other (F. C.) at 15 months after therapy with 1.39 gm. Both responded to retreatment with 0.5 gm., although the response was incomplete

FIG. 1. Patient J. H.: Cutaneous lesion before therapy with amphotericin B.

in F. C., who refused further therapy. In the other patients, no recurrences have been seen over periods ranging from one to 25 months after completion of therapy.

Of the 17 patients, therapy was ineffective in three. One (J. L.) received only 10 mg. intravenously, and should be excluded from further consideration. Only one patient given amphotericin B died as a result of

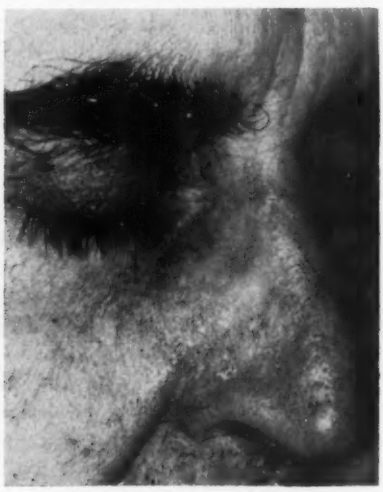

FIG 2. Patient J. H.: Complete healing of cutaneous lesion after 930 mg. amphotericin B.

blastomycosis: P. H. had diffusely disseminated disease, and died after 13 days (640 mg.) of therapy. In this interval, cutaneous and joint lesions had improved greatly, but he died suddenly after a massive spontaneous pneumothorax. At autopsy, abscesses containing blastomyces were found in the lungs, larynx, heart, spleen, kidneys, adrenals, and prostate. The other patient without response (A. T.) had a single cavitary pulmonary lesion which had persisted despite two courses of 2-hydroxystilbamidine and excisional surgery. This patient was killed in an accident two months after therapy.

Comments

The response of this group to amphotericin B has been gratifying. However, the proper evaluation of results is made difficult by the fact that blastomycosis is often a chronic infection, characterized by remissions and exacerbations. Accordingly, long periods of observation are necessary for adequate evaluation of any agent used in this disease. It is therefore possible that the rate of recurrence in these patients may be higher with further observation.

The determination of the optimal dosage of amphotericin B in blastomycosis must necessarily await continued study. In this group of patients, although two made excellent recoveries after only 300 and 680 mg., respectively, two other patients had recurrences after receiving more than 1 gm. Harrell and Curtis [7] also noted that, of seven patients given an initial course of 1 gm., two had recurrences. In our seven patients who received approximately 2 gm. or more initially, no recurrences have been seen during an average follow-up of nine months. From these combined experiences, it is our present recommendation to treat initially with a course of 2 gm. of amphotericin B if the agent is well tolerated by the individual.

Unfortunately, the toxicity of this agent, particularly in azotemia, often requires interruption and prolongation of therapy. Since the azotemia and cylindruria are usually promptly reversible and not permanent, therapy may be continued even when they are present. This view is confirmed by the detailed studies of Beard et al.,[2] who found that the depressed renal function uniformly recovered after therapy had been completed. Although the administration of amphotericin B on alternate days may reduce the toxic reactions, it is not certain whether this will be as effective therapeutically. Further experience is needed to answer this question.

Although no strict comparison of the effectiveness of amphotericin B with the results of diamidine therapy can be made, an analysis of 10 patients from this hospital treated intravenously with a diamidine (stilbamidine, 2-hydroxystilbamidine, or aminostilbamidine) showed that those patients given amphotericin B had a faster onset of improvement, a higher incidence of good results, and fewer recurrences after completion of therapy. Harrell and Curtis [7] also report that amphotericin B was effective in eight patients who had responded poorly to diamidines. Certainly there can be no question

that amphotericin B is a potent agent in the therapy of blastomycosis. Indeed, the combined experiences reported so far (apparent cure in 88% of 43 patients) would suggest that amphotericin B is more effective than the diamidines, and that it is the agent of choice for the therapy of North American blastomycosis.

Summary

Seventeen patients with North American blastomycosis have been treated with parenterally administered amphotericin B. Of the 16 receiving adequate therapy, one patient died while on treatment, and another showed no change. Fourteen patients experienced prompt healing with therapy, but two later had recurrences of their disease, and another died of other causes shortly after therapy. The remaining 11 individuals have been followed for an average of 13 months, without recurrence. Toxic reactions to amphotericin B were frequent, and in two patients therapy had to be discontinued because of renal toxicity; however, no permanent renal damage has been recognized.

Summario in Interlingua

Le effecto de amphotericina B esseva evalutate in 17 patientes con blastomycosis nord-american. Le majoritate del patientes habeva disseminate infectiones e un responsa immunologic—negativitate del test cutanee e positive reactiones serologic—associate con un prognose pauco favorabile.

Un patiente esseva tractate con amphotericina B per via oral, con un resultante melioration de character dubitose. Inter 16 patientes recipiente un adequate therapia per via intravenose, 14 respondeva con prompte curation. Un patiente moriva durante le tractamento; un altere manifestava nulle effecto. Recidivas occurreva in duo patientes. Un altere moriva ab altere causas brevemente post le therapia. Dece-un del patientes esseva tenite sub observation durante un periodo medie de 13 menses sin signo de recurrentia. Le optime dose total de amphotericina B non poteva esser determinate criticamente, sed nulle recurrentias esseva notate in septe patientes qui recipeva approximativemente 2 g.

Reactiones de toxicitate contra amphotericina B esseva frequente. Le plus serie esseva un effecto nephrotoxic. Isto occurreva in 12 casos. In duo patientes, iste effecto necessitava le interruption del therapia. Le melioration occurreva rapidemente, in despecto del interruption temporari o del cessation del therapia, e nulle permanente vitiation renal esseva recognoscite.

Iste resultatos—conjunctemente con previe reportos—indica un cura apparente post amphotericina B in 88% de 43 patientes con blastomycosis. Tal resultatos es plus favorabile que illos obtenite con diamidinas e suggere que amphotericina B deberea esser considerate como le agente de election pro le therapia de blastomycosis nord-american.

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An Address

REFLECTIONS FROM OUR MIRROR*

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It is a privilege and a pleasure for me to participate in this delightful and significant ceremony of the Gold-Headed Cane. To him who receives the cane and to those who are honored by mention, I extend my congratulations. This is an honor and a distinction that you should cherish forever.

That this award is unique and at the same time of deep significance was expressed by your respected Professor of Medicine Emeritus, Dr. William J. Kerr, when he wrote in 1953 in the preface of the book, *"The Gold-Headed Cane,"* these words: "The award is based upon the student's interest in the welfare of his patients during his entire clinical experience. . . . The award serves to augment and embellish other rewards of recognition for scholarship, which are generally announced at the termination of many years of theoretical and practical education, by emphasizing the fact that its recipient possesses those qualities inherent in the well-educated physician."

These remarks helped me crystallize what I wanted to say to those of you who will soon be graduated from this great University Medical Center to pursue your lives in Medicine. Increasingly in the future, there will rest upon your shoulders, and those of your contemporaries, the sobering responsibility for the advancement of Medicine and for keeping untarnished the standards and the image of Medicine. The image of Medicine in the public eye is not so much concerned with buildings, institutes or public pronouncements of our accomplishments, but more with the skill, compassion and human understanding we bring to the sick and injured. In addition, a physician is instinctively assumed to be a man of dignity, scrupulous morals and principles, and education.

That the public seems to feel we have fallen short of this image of us is evident. We are worried by this, and all earnest physicians are bewildered and frustrated by the attacks made upon us. We have poured money and effort into fruitless devices such as "public relations" campaigns and other similar measures designed to convince the public of our high purposes. However, when the eyes of the public are perceptive, these activities are doomed to failure. What is of far greater importance is that we

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recognize that today we are less close to our patients than we should be and that we have not taken into full account, as individual physicians, that we and our times have changed.

We have changed because research has provided us with a far greater depth of understanding of man, his diseases and their treatment. We have changed because our new and fascinating technology has tempted us to depend upon it more and more, with a resultant decline in some of the indispensable parts of the art of medicine. We have changed because social and economic forces, often difficult for us to accept, adjust to or understand, have modified greatly our way of life. We have changed because in our enthusiasm for everything new we have tended to jettison some of our most important and time-tested knowledge and skills. I would like to discuss some of these changes and their significance, as well as other related matters.

You who are about to carve your career in Medicine and cast your own image, I ask to "look into our mirror" with me and think about some of the problems we shall see. Let me say, no matter what my words may suggest, I am not an elder who looks back only at the past. On the contrary, I believe and live in the present, and I look forward to the future with as much interest, excitement and anticipation as you. What does concern me is, that as we move forward at an ever accelerating pace, we keep education, research and practice in balance and our perspectives clear.

After spending more than thirty years teaching students, interns, residents and doctors, and having enjoyed an illuminating experience with the American Board of Internal Medicine, I have discerned some trends in modern medicine and medical education which disturb me. I want to interest you in these, because you will have to be concerned with them, whether you become a practitioner, a teacher or an investigator. I believe these are of great importance in our behavior and effectiveness as doctors, and, not the least, in our relationships with our patients.

We are sagging badly in our skill as historians. Everywhere one sees a decline in interest in hearing through a patient's whole story. The excuse is made that there is too little time available, so short-cuts and devices in history taking are sought and constructed, even though none can ever approach the performance of a knowledgeable, thoughtful, and interested physician. The art of listening and the *willingness* to listen is one of the precious assets of a fine physician. This does more to cement the physician and patient together than anything else. To listen intelligently requires depth of knowledge, imagination, an open mind, a critical sense of values, and human understanding. To do this well requires time. If we will but listen, the patient will often tell us the diagnosis, and will uncover what his illness has done to him as a person, his fears, and the tortures of his mind.

We must be cautious about labeling a patient a "poor historian." We have a tendency, when dealing with vague complaints like the description of

paresthesias or the dawning of symptoms of an early pancreatic carcinoma or a brain tumor, to turn our sense of frustration toward the patient. We fail to recognize that the trouble may lie in us, in our inability to comprehend or analyze the truth we hear. It is humbling for any of us to try to put into clear language some of our own vague complaints. There are no shortcuts along this road, no satisfactory substitutes are now or in the future will be available. Nothing can take the place of this precious kinship between patient and doctor. We must develop and preserve our willingness to listen and the skill to do it well, and we must be prepared to take the time that it requires.

Related to this is an alarming ineptness in physical examination that one sees at every hand. No doubt this is a product of our technological age and the increasing preoccupation of the staffs of our medical schools with technology and research. Beating upon this well worn subject seems to stamp one immediately as a full-flowered stand-patter, an unreconstructed, unimaginative member of the Old Guard. Yet I know what competent physical diagnosis can offer, and for that reason I am concerned with its decline. To those who minimize the value of physical diagnosis there is a simple answer—they just are not expert in the field.

Physical examination is not a ritual, it is not the performance of a certain number of motions. It must be a study, by the means of our senses, of those evidences of normal and abnormal anatomy, physiology and biochemistry that can be detected by them. Unless we have eyes that truly see the surface of the skin, and beyond; disciplined and perceptive fingers sensitive to the slightest changes; ears that not only hear but understand; and an alert and knowledgeable nose, we can never be competent in this art. Good physical examination, too, requires more than the usual foggy remembrance of anatomy that is shared by so many of our graduates today. At the end of a good history and a competent physical examination, often we have gone the distance in the diagnostic study of a patient, laboratory examination being only confirmatory or even unnecessary. When further study is required, we are in the enviable position of being able to call upon our technologic and other aids with precision and without waste of time and money.

It is hard to understand why, in many medical schools, the teaching of this indispensable art is, for the most part, left to young men. Young men are eager and often effective teachers, but they too are still learning and have not had the tempering in this area that only time can provide. The years required to acquire excellence in physical diagnosis calls for the participation of our most experienced staff in the teaching of this subject. And we should take care that we do not cast the novice loose after his sophomore course, but continue to emphasize the subject through every level of his subsequent training. We need to stand aside from our preoccupation with enzyme activity in the renal tubules or the dance of ions through the myo-

cardial cell membrane long enough to make sure our budding physician can palpate adequately a cardiac apex beat and in doing so derive some useful information.

As I have read through countless clinical records in my own hospitals and in other hospitals all over this land, the mayhem that is being done to our mother tongue has been painfully evident. We have been seized by the same obsession for initials or word "gimmicks" that is current everywhere, especially in government. Charts are full of symbols, letter abbreviations, arrows pointing in all directions and even weird drawings, purported to be a clear way of portraying neurological findings. Actually, these more closely resemble prehistoric art left behind in caves by our ancestors. Good English in clinical records is becoming scarce, good handwriting even more so.

We use and re-use hackneyed words such as "reveal," "downhill," "presented," "picture," "developed," and many others. We "place" patients *on* a medication. We make verbs out of nouns. We seem to love the ending "-ize." How often do we hear that a patient has been diuresed, splenectomized or anticoagulated (a rather horrible state to contemplate)? A familiar classic around our institution is the patient who has been "turped." For those of you who may not recognize this sterling contribution, the patient has received a transurethral prostatectomy! And "PERLA," noted in the physical examination, tells you the pupils are equal and react to light and accommodation. I have fought long and hard against this demoralizing trend, but I must confess to a weariness with the battle and a sense of fighting a rear guard action.

Too much of the published American medical literature is stilted, stuffy and plain hard to read. The format of medical articles is more and more in a strait jacket so that they are coming to look like carbon copies of each other. Abbreviations and initials, clear to the author but unfamiliar to the reader who must constantly remind himself of what they mean, clutter the pages and impose endless roadblocks to the reader's progress.

It is unusual to find an American article that is *fun* to read and which by the very excellence of its prose and arrangement stimulates one to read on to its very end. What a contrast many of our colleagues in England provide! So often their writing is elegant, relaxed, free from tangle-footed construction and beautifully clear. Many authors give the impression that if they do not follow a rigid pattern of writing and fail to lard their manuscripts with bewildering formulas, overloaded graphs, and mathematical equations (which, if I may say parenthetically, I suspect sometimes are understood only by the institution's statisticians), they will be regarded as unscientific. It is necessary, of course, that scientific data be presented, but at the same time it is sad that many authors who have something to say that is of importance to many physicians, succeed in making their contributions comprehensible only to a few who work in their particular field.

Why is this? I believe a large segment of the trouble is related directly to a deficiency in the broad, liberal education of our students. How many students who enter medical school have tasted adequately of English, literature, history, art, philosophy, language? Too many have spent their collegiate time in science. Many medical schools give lip service to a liberal education as a preparation for Medicine, but impose such stringent requirements in science that students cannot wholly be blamed for the course they pursue. While training in science is of vital importance in Medicine, we cannot escape the fact that a Doctor of Medicine, by the very nature of his profession, needs to be a broadly educated person. Broad education does not come from an exclusive devotion to the study of science.

We are awakening to this problem, and the efforts of some medical schools to intermix liberal education in the early period of medical training are interesting. However, too frequently this is done with the idea of telescoping the time required to complete the collegiate and the medical course. I do not feel optimistic about the eventual rewards of such an approach. I quite agree that the road of medical training is long and expensive, and wherever possible it should be shortened. But I must confess that I have the firm conviction that telescoping collegiate and medical training will result not in true *physicians,* but in technologists who lack the breadth of education and the grace that is essential in a Doctor of Medicine. I can speak feelingly about this, because I had four years of strictly technical education in engineering before I entered medical school.

During our current deep concern with our educational programs we must stop, take a hard look and ask ourselves the question: "Do we want technologists of medicine or Doctors of Medicine?"

Medical teaching has undergone considerable change. Today we find ourselves preoccupied with "integrated" programs and such, with not enough attention being paid to the number and quality of our teachers and where they will come from. Where we will get *good* teachers to staff the greatly expanded medical school facilities of the future is a problem of acute and major significance. Teaching is coming to be a by-product, an afterthought, and compared to research is currently regarded as of low caste. Broad-based teachers are rapidly fading from the scene, but, paradoxically we still revere the memory of Osler whose greatest contributions lay, really, in teaching and writing in the broad field.

There is almost no place in medical schools today for the young man possessed of that rare capacity to teach well, whose interests lie not in the laboratory but in the study of disease in the patient, and whose understanding of medical knowledge includes a desire to pass this on to students of medicine. I have encountered a number of young men of this caliber who have been interested in an academic career. Supremely bright individuals, their interests were in study and teaching in the wards and the classroom. They could work in the laboratory, yes, but they had no strong heart for it

and their talents were not in that direction. They could contribute mightily by the clinical study of disease, but this effort nowadays, unfortunately, is not highly regarded in academic circles. I had to discourage these men from such a career because they could never accumulate a "bibliography" large enough to make them attractive, nor did they want to run a laboratory. Furthermore, I knew that, while they would do a superb job of teaching, the volume of their publications would not be great enough to permit them to advance far in the academic world. They could not attract grants to help support their activities and broaden themselves by travel to other institutions. The tradition of "publish or perish," now so strongly rooted in our schools, has contributed in no small way to the padding of our literature with unimportant material and has deprived us of men who, while good but less voluminous writers, would be invaluable in teaching.

The phenomenal expansion of research in the past twenty years has been a strong factor in the reorientation of the roles of teaching and research in medical schools. No one in his right mind would want to retard the advancement of research, although there are plenty of instances where its quality could be improved. My only complaint is that as of now, research and teaching are out of balance, and it is time we did something about it. Hundreds of millions of dollars of public and private funds are provided each year to support research and research facilities, while only a pittance is available to medical education. We talk in grandiose terms about research programs to "wipe out cancer" or "eliminate heart disease," but who, unless we have an abundant supply of well trained physicians, is going to apply all this new knowledge for the benefit of the sick?

The growth of our knowledge, together with the fact that it is becoming more difficult to comprehend, has given impetus to heavy sub-specialization. At present most of the load of teaching in our schools is borne by investigators and sub-specialists. Not all good investigators are good teachers, no matter what fond hopes to the contrary may be held. And, when we teach by sub-specialties, we prepare our students to comprehend the whole by giving them only vignettes of its parts.

Sub-specialists may be superb teachers in their respective areas, and we will always need their teaching in our overall training. However, when most sub-specialists get into the peripheral portions of their specialties—a no man's land where overlap with other specialties occurs—the sub-specialist is handicapped. His viewpoint and his knowledge is too restricted to make him really effective here. It is in this situation that the broad-based teacher is at home. While the latter does not have the depth in each sub-specialty as does the sub-specialist himself, he can deal with most situations effectively and can keep the broad approach before his students. When he is teamed with the sub-specialists in a common effort, we have the ideal in teaching. The President of our University expressed this dilemma well recently when he indicated we must take care, in this day of specialization, lest we turn

out products from an educational assembly line that have two or three power plants, two or three rear ends, and no steering wheel.

Research is a vital obligation and function of a medical school. But so is teaching and patient care. The time has come to do more thinking about the "school" and see how research is really wagging the whole dog. Research must be nurtured, and it must expand. Its influence must be felt through the whole of a medical institution if it is to be alive. However, the time may be coming and we may be better off if most, but, of course, not all, research is carried on in a research institute, connected with the medical school, which has its own staff and only a nominal responsibility for teaching. This would make it possible to develop a teaching staff which could dedicate more time, in an uncluttered atmosphere, to the broad duties involved in education and service and less time in research. I know this pill will not be swallowed by most men in academic positions, but bear in mind I do *not* advocate that investigators be cut off from contact with students or that students be cut off from them. Some change like this will be necessary if we are to keep our educational processes at peak efficiency and in proper perspective.

We must recognize that top-flight medical teachers are as much born to their particular talents as are investigators; that to be a fine teacher requires brilliance, time and deep study; that excellence in research and excellence in teaching are not necessarily synonymous nor, from the standpoint of the individual's being able to exploit his talents to the fullest, compatible.

This long discourse may seem to be no more than lamentation and complaint. I have not advanced many solutions, because some are, as yet, unclear. I have tried to bring to you and clarify for you some problems that cry for a solution, problems to which you should apply your thoughts and energies. These are matters of importance for the present, as well as for the future. The decisions you and your contemporaries make will have a profound effect on the future progress and stature of Medicine. But, if you keep before you the guiding principles and thoughts that inspired the concept of the Gold-Headed Cane, I will have confidence in your part of this future.

CLINICAL PATHOLOGICAL CONFERENCE

UNEXPLAINED DEATH IN A PATIENT WITH LEUKEMIA: CLINICAL PATHOLOGICAL CONFERENCE AT THE NATIONAL INSTITUTES OF HEALTH *

Moderator: CHARLES G. ZUBROD, M.D. *Discussants:* LEON ROSENBERG, M.D., N. RAPHAEL SHULMAN, M.D., VERNON KNIGHT, M.D., WALLACE P. ROWE, M.D., JOHN EDGCOMB, M.D., and T. F. HILBISH, M.D., *Bethesda, Maryland*

DR. CHARLES G. ZUBROD: Dr. Leon Rosenberg, of the Metabolism Service, National Cancer Institute, will present the clinical findings, and we have asked two clinicians from other Institutes to discuss the problem. Then Dr. John Edgcomb, Pathologic Anatomy Branch, National Cancer Institute, will present the autopsy findings. In addition, we have an invited speaker, as yet unnamed, who does know the diagnosis, and who will tell us more about some of the specific findings from the research viewpoint.

DR. LEON ROSENBERG: This 37 year old white male State Department Foreign Service officer noted the onset of weakness, easy fatigability, headaches, and anorexia in November, 1956. In January, 1957, he became aware of a mass in the left upper quadrant of the abdomen and consulted a physician in Vienna, Austria, where he was stationed. A report from that clinic states that the patient presented with pallor, numerous skin petechiae, and massive hepatosplenomegaly. Laboratory data obtained in March, 1957, showed hemoglobin, 50%; white blood cell count, 430,000; platelet count, 200,000; and bone marrow aspiration "compatible with chronic myelogenous leukemia." The patient was treated with a single intravenous dose of 55 mc. of radioactive gold (Au^{198}), and within two weeks had noticed subsidence of weakness as well as regression of splenomegaly. By April, 1957, the white blood cell count had fallen to 156,000.

In June, 1957, the patient returned to the United States and was seen in the outpatient clinic of the Clinical Center of the National Institutes of Health. The spleen was felt 5 cm. below the left costal margin in the midclavicular line, but the remainder of the physical examination was entirely unremarkable. On July 28, 1957, he was electively admitted to the Clinical Center for evaluation. Family, personal and social histories were noncontributory, and complete system review was unrevealing. Positive physical findings included only a liver palpable 2 cm. below the right costal margin, and a spleen palpable 7 cm. below the left costal margin. Laboratory data on admission: hemoglobin, 14.7 gm.%; hematocrit, 43%; platelet count, 248,000; white blood cell count, 50,000, with 66% mature polymorphonuclear leukocytes, 12%

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nonfilamented polymorphonuclears, 10% metamyelocytes, 3% eosinphils, 2% basophils and 1% myeloblasts; serum uric acid, 6.2 mg.%. Bone marrow aspiration showed a myeloid: erythroid ratio of 10: 1, with a predominance of myelocytes.

On August 12, 1957, while being followed in the clinic, the patient was started on 4 mg. of Myleran per day. By November, 1957, the spleen had become barely palpable, and the white blood cell count had fallen to 11,000, with a normal differential. For the next nine months the patient did very well on continuous Myleran therapy, the dose ranging from 1 to 7 mg. per day, depending upon the blood count. However, in August, 1958, he came to the clinic complaining of slight dyspnea on exertion and mild ankle swelling. The spleen was found to be 14 cm. below the left costal margin. Blood count showed: hemoglobin, 9.5 gm.%; white blood cell count, 11,300; platelet count, 80,000.

In the face of anemia, thrombocytopenia and increasing splenomegaly, the patient was re-admitted to the Clinical Center on August 19, 1958. Physical examination revealed posterior cervical and axillary lymphadenopathy, a spleen palpable 20 cm. below the left costal margin and extending across the mid-line into the right lower quadrant, a soft precordial systolic heart murmur, and 1-plus pitting edema of both ankles. Laboratory values at this time: hemoglobin, 8.3 gm.%; hematocrit, 27%; platelet count, 102,000; white blood cell count, 10,200, with 80% mature polymorphonuclears, 4% nonfilamented polymorphonuclears, 3% metamyelocytes and 10% myelocytes; reticulocyte count, from 2 to 5%; blood urea nitrogen, 13 mg.%; serum uric acid, 5.6 mg.%; serum albumin, 2.6 gm.%; serum alkaline phosphatase, 5.1 Bessie-Lowry units; bromsulfalein retention, 10% in 45 minutes; cephalin flocculation, thymol turbidity and prothrombin time, normal. Bone marrow aspiration again showed a marked predominance of cells of the myeloid series, with few normoblasts or megakaryocytes.

On August 25, 1958, the Myleran was stopped and therapy begun with 60 mg. of 6-methyl-delta-1-hydrocortisone (Medrol) per day. By September 4, 1958, the white blood cell count had risen to 90,000, and therapy with trimethyl colchicinic acid (TMCA), at 6 mg. per day, was added. The white blood cell count continued to climb, reaching 224,000, with 5% "blast" forms, by September 8, whereupon the Medrol was discontinued and the TMCA increased to 12 mg. per day. By September 12, 1958, the white blood cell count had fallen to 3,200 and the platelet count to 10,000, whereupon the TMCA was discontinued and all further chemotherapy withheld.

On September 8, 1958, rectal temperature (which previously had been normal) rose to 39° C. Physical examination and chest x-ray revealed no obvious cause for the sudden pyrexia, and cultures of the throat, urine and blood were unrevealing. For the next 15 days the temperature rose to from 38.5 to 39.5° C. daily. No etiology for the fever could be found, despite exhaustive investigation. From September 23 to October 10 the patient remained entirely afebrile and his condition seemed to improve. During this period the white blood cell count rose to 65,500 and the platelet count to 170,000. The spleen remained from 15 to 20 cm. below the left costal margin and was exceedingly tender. In an attempt to shrink the massively enlarged spleen, a course of splenic radiation was undertaken on October 20, and the patient received a total of 675 r in 10 days. This therapy was not followed by any demonstrable reduction in spleen size, but a transient fall in the white blood cell count to 28,000 was noted.

The patient's course changed abruptly on October 30, 1958, when his temperature again rose to 40° C., and distinct redness and swelling of the entire left lower extremity appeared. Conservative therapy was instituted for thrombophlebitis, but anticoagulants were withheld. Persistent fever and left leg signs remained unchanged until the evening of November 4, 1958, when the patient suddenly complained of severe dyspnea. Fine inspiratory râles were audible over the right and left lower

lung fields posteriorly, and a chest film showed "bilateral infiltrative lesions in both lower lung fields." Cultures were obtained and the patient was started on nasal oxygen, penicillin and streptomycin. His condition stabilized for 10 hours, whereupon he suddenly gasped and died while being turned in bed.

A sputum culture obtained just before death grew out a mixed flora including hemolytic *Staphylococcus aureus* sensitive only to erythromycin and Albamycin. The blood count on the day prior to death was as follows: hemoglobin, 7.6 gm.%; white blood cell count, 58,000; platelet count, 34,000.

DR. T. F. HILBISH: I will show only two chest films, since the other films do not contribute to the discussion. A film taken in August, 1958, is shown

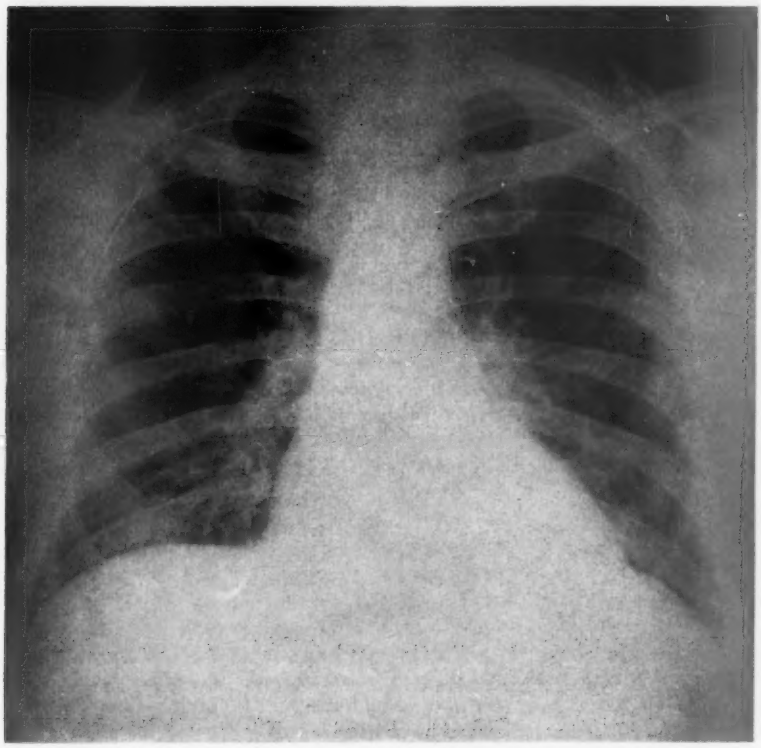

FIG. 1. X-ray film of chest taken in August, 1958, before development of fever.

in figure 1. Subsequent films show no significant abnormality until the film of November 4, 1958 (figure 2), taken immediately prior to death, at which time there has been a very decided change in the radiologic appearance. The midlung fields are now diffusely infiltrated. On close inspection, small nodular areas of increased density can be noted. From a radiologic standpoint a number of possibilities would be considered, one, of course, being a disseminated bronchial pneumonia. The radiologist who read this film thought immediately in

terms of pulmonary edema, particularly of the type seen in uremia. A number of other possibilities could be considered, such as lymphogenous spread of neoplasm, leukemic infiltration, extensive infarction and viral pneumonia.

The purpose of presenting these two films was to show the dramatic change in the radiologic appearance of the chest immediately prior to death.

Question: Was it considered that any of these patches show cavitation?

DR. T. F. HILBISH: No, no definite cavities were recorded.

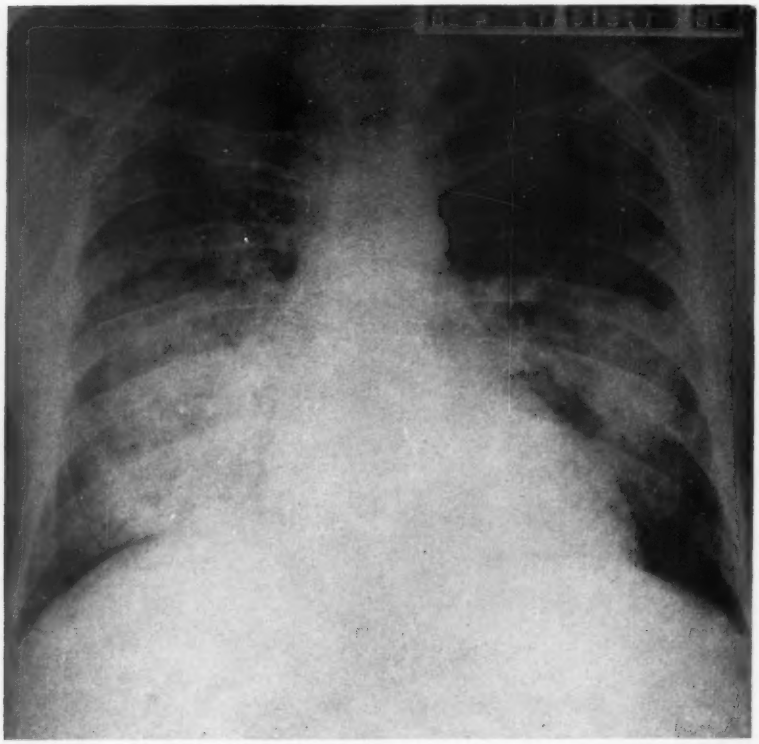

FIG. 2. X-ray film of chest taken on November 4, 1958, one day prior to death.

Question: Was there increase in heart size?

Dr. T. F. HILBISH: There was, but not to an abnormal degree. I did not measure the heart exactly, but it was within the range of normal. Just to orient you on this: the heart may vary in size in transverse diameter as much as 2 cm. between systole and diastole, so that in this case the change was well within the physiologic range.

DR. CHARLES G. ZUBROD: This patient with leukemia, in addition to the hematologic aspect of his problem, suffered a terminal event consisting of fever and pulmonary disease. I have asked Dr. Raphael Shulman and Dr. Vernon Knight to discuss these aspects of the patient's illness. I should like now to

call on Dr. Raphael Shulman, who is head of the clinical investigations hematology group of the National Institute of Arthritis and Metabolic Diseases, to open the discussion.

DR. N. RAPHAEL SHULMAN: The mode of onset of this patient's disease, the presenting complaint, the initial blood counts and bone marrow taken in March, 1957, were all quite typical of chronic granulocytic leukemia. The finding of a 50% hemoglobin concentration at the time probably indicated that the disease was fairly well advanced, for anemia in this form of leukemia characteristically does not appear until many months or even a year or two after high leukocytosis and splenomegaly have been present.

It also should be mentioned that the finding of numerous skin petechiae when the platelet count was normal is not unusual in chronic granulocytic leukemia. Hemorrhagic manifestations may occur even in the presence of a normal or elevated platelet count in this disease. It is not at all clear why this happens, but it may possibly be related to abnormally functioning platelets, for which there is no laboratory test.

The initial remission, which was excellent, was induced by total body radiation in the form of intravenous radioactive gold, an isotope infrequently used in this country. The same results would no doubt have been obtained with spray x-ray, P^{32}, or local x-ray to the spleen, or any of a number of chemotherapeutic agents, particularly the nitrogen mustard-like compounds.

The remission lasted for approximately five months, the expected period for the first induced remission being from three to 18 months. Toward the end of the five-month period, in spite of the patient's apparent well-being, the white count was beginning to rise, the spleen was enlarging, and the bone marrow was typically leukemic. He was then given Myleran for an entire year. Myleran, a sulfone used orally, is a nitrogen mustard congener. It appears to have a highly selective effect against granulocytes, and has been found to be one of the more effective agents in the treatment of chronic granulocytic leukemia.

The second remission, which is usually shorter than the first, actually was longer in this instance. However, after a year on variable daily doses of Myleran, the patient developed exertional dyspnea and mild ankle swelling associated with anemia. The low serum albumin, the slight phenolsulfonphthalein retention and the systolic murmur were in keeping with the anemic state. Thrombocytopenia was not significant. Severe anemia, rapid massive splenic enlargement and the appearance of palpable nodes during August, 1958, could be considered to be ominous signs, for these manifestations may herald the beginning of the end in chronic granulocytic leukemia—that is, the resistant phase which does not respond favorably to any form of treatment.

At this point, perhaps to combat progressive anemia, the steroid Medrol was given. Steroid hormones are actually myelo-stimulatory, and treatment of complications of chronic granulocytic anemia with steroids is controversial because, if they do not help, they may harm. Their use is usually limited to the treatment of chronic lymphocytic leukemia or the acute leukemias, in which they may either produce remissions of the leukemic process itself, or, in the case of lymphocytic leukemia, at least benefit the frequently associated "autoimmune" Coombs-positive hemolytic anemia. Although it is not entirely cer-

tain, steroid therapy in the present case may have stimulated the leukemic process and produced a higher percentage of blast forms in the peripheral blood.

At the peak of the leukocytosis the patient had a febrile spike to 102° F., followed by a 15-day period during which there were temperature elevations of 101° to 103° F. This apparently was a swinging rather than a sustained fever. There was no obvious cause for the pyrexia, but one wonders whether it might have been at least in part a manifestation of splenic infarction.

At some time between September 8 and the next mention of the spleen, October 20, splenic infarction no doubt took place, for the spleen became quite tender. Splenic pain in chronic granulocytic leukemia is practically pathognomonic of infarction, and infarction occurs at some time in one third of such cases. A huge spleen may cause other symptoms, owing to weight alone or to pressure, but becomes tender almost without exception only when infarcted. Because infarction of the spleen in leukemia is best explained either by encroachment of masses of myelocytic cells on blood vessels, or by so-called outgrown blood supply, the best timing for such an occurrence would be around September 8, when myelocytic elements were rapidly increasing.

A single infarction, unless massive, and then usually associated with friction rub and other objective signs, would not account for 15 days of fever, but multiple splenic infarcts are not uncommon. On the other hand, leukemics in relapse may have daily temperature elevations of 101° F. or 102° F. without underlying complications.

To summarize the point, the fever which began on September 8 seemed a little too high for leukemia alone, and more prolonged than expected for infarction of the spleen alone, but the combined processes could explain it, particularly in view of the negative blood cultures and the absence of signs of infection, and in view of the subsequent defervescence when the colchicine derivative produced a marked fall in the white count.

At this stage of leukemia, any myelotoxic agent which suppresses white cell formation usually suppresses platelet formation as well. The ensuing severe thrombocytopenia necessitated numerous transfusions of fresh whole blood to control hemorrhagic manifestations. The response to trimethyl colchicinic acid was further evidence that the disease had become uncontrollable, for even the profound suppression of marrow which was produced did not result in a significant remission or a change in the spleen size.

Beginning October 20, the spleen was irradiated in an attempt to shrink it. This treatment was ineffectual, although the amount of irradiation given would have been sufficient to cause prompt regression in spleen size as well as general improvement if the patient had been in a responsive phase of the disease. The day radiation therapy was stopped the patient developed a sudden fever of 104° F., associated with redness and swelling of the entire left leg. The fever and leg signs persisted, but apparently no other prominent signs or symptoms developed until five days later, when the patient complained of severe dyspnea. If I interpret correctly, this dyspnea was quite transient, for his condition stabilized that same night. However, 10 hours later he died very suddenly in the process of being turned in bed.

In interpreting the events during the last five days of life, one is tempted by the fact that this is a clinical pathological conference to explain the picture on some basis other than thrombophlebitis and pulmonary embolism. Rather

than that, I would prefer to discuss the features which seem to make thrombophlebitis with a terminal pulmonary embolus the most likely diagnosis. I cannot say that I was not upset by Dr. Zubrod's introductory comments, but if it does not prove to be a thrombo-embolic phenomenon, at least whatever happened certainly mimicked it.

Patients with leukemia, as a group, are prone to develop deep thrombophlebitis. If, however, it is considered that thrombocytopenia should have protected against the development of thrombophlebitis, it should also be considered that the tremendous spleen may well have been large enough to produce pressure at the pelvic inlet and, by slowing the flow in the iliofemoral veins, particularly on the left side, predispose to thrombosis even in the presence of thrombocytopenia.

For some reason there seemed to be hesitancy to make a definite diagnosis of thrombophlebitis, and no anticoagulant therapy was given. Perhaps this was due to the unusually high fever associated with the leg involvement. Constitutional reactions with thrombophlebitis are quite variable and, although fever higher than 102° F. is infrequent in the usual case of thrombophlebitis, the febrile response of a debilitated leukemic may have been exaggerated. The appearance of the leg in acute iliofemoral thrombophlebitis may in some respects resemble that of acute diffuse lymphangitis or cellulitis initially, but the latter diagnosis would not have been obscure for long. Perhaps Dr. Knight will comment further on that differential possibility.

With thrombophlebitis in a major vein, once the inflammatory component is clinically evident and has persisted for three or four days, there is very little danger of fatal embolism, for the large thrombus which has already formed is firmly adherent to the vein walls; but there may be relatively minor embolic episodes from small fragments of a newly propagated clot at the end of the thrombus. If the patient has not yet had an embolism and receives adequate anticoagulant therapy, even minor nonfatal embolic episodes almost never occur.

Unfortunately, fatal emboli from large veins usually precede the development of clinical signs of thrombophlebitis. Statistically, in a series of over 300 cases of fatal pulmonary embolus studied by Barker[1] at the Mayo Clinic, only 15% had clinical evidence of thrombophlebitis in any vein preceding death, and only 5% had clinically diagnosed iliofemoral thrombophlebitis.

In the present case, therefore, the assumed large adherent thrombus in the left iliofemoral vein probably could not account for the fatal episode, but detachment of a fragment of newly propagated thrombus could account for the episode of severe dyspnea which occurred the day before death. A recent, relatively small embolus notoriously can be difficult to diagnose on the basis of objective signs by physical examination, x-ray or electrocardiogram, but may produce symptoms such as dyspnea which are out of proportion to the clinical findings. The symptoms may result from reflex bronchial spasm or pulmonary arteriolar spasm. In this patient with longstanding marked anemia and the likelihood of associated heart disease, the further insult of even a small pulmonary embolus could have precipitated acute pulmonary edema. The acute dyspnea passed quickly. Rapid mitigation of acute symptoms occurs characteristically with small pulmonary emboli, and is explained by subsidence of the reflex physiologic changes provoked in the bronchi and pulmonary arterioles. Improvement occurred too quickly to be accounted for by the administration of

antibiotics, particularly since the sputum grew out organisms insensitive to the antibiotics that were given.

I had wished to explain the fine respiratory râles at the bases and the infiltrative process described in the protocol on the basis of compression partial-atelectasis caused by the enlarged liver and spleen; but the x-ray film shown by Dr. Hilbish is not consistent with this. If not due to pulmonary edema, the x-ray changes might be explained by bronchial pneumonia. It may be of some help to have some data on the sputum. Do we have any information on the sputum?

DR. JOHN EDGCOMB: It was not reported to be grossly purulent sputum or rusty.

DR. N. RAPHAEL SHULMAN: Was there much?

DR. JOHN EDGCOMB: Scant amounts only.

DR. N. RAPHAEL SHULMAN: Well, that is not very helpful, but is in keeping with the possibilities mentioned.

About 10 hours later it can be assumed that the patient died from a massive embolus, death apparently occurring immediately. An embolus large enough to produce immediate death probably would not have come from the adherent thrombus in the left iliofemoral vein, and probably not from any clot which could have propagated from the thrombus in that vein. It most likely came from the right iliofemoral vein, in which a fresh thrombus had formed that had not yet caused clinical symptoms of thrombophlebitis. One could guess that an embolus might have been released as a result of decreased pressure from the spleen if the patient was turned toward the left side.

It should be mentioned that there are some rare, acutely fatal occurrences which have been reported at least once in association with chronic granulocytic leukemia—for instance, extensive leukemic infiltration of the auricle or descending aorta leading to rupture of these structures, infiltration of the interventricular septum resulting in complete heart block, and also rupture of the spleen—but these are medical oddities not diagnosed ante mortem.

My diagnoses would be: myelocytic leukemia, left iliofemoral thrombophlebitis, one relatively small pulmonary infarct of recent occurrence, and a very large embolus occluding the pulmonary arteries (the embolus would most likely be a thrombus cast of peripheral veins, showing no organization), multiple old splenic infarcts, nonspecific basilar pneumonitis, and, in view of the x-ray changes, probably bronchopneumonia.

DR. CHARLES G. ZUBROD: Thank you, Dr. Shulman.

I should like now to ask Dr. Vernon Knight, the Clinical Director of the National Institute of Allergy and Infectious Diseases, to continue this discussion.

DR. VERNON KNIGHT: After this excellent discussion of the course of leukemia, it seems perfectly clear that that is what the man had, and it was not a very surprising course of events, except that he died more quickly than usual . . . unless he had had a blastic crisis, which was not identified. Moreover, the terminal febrile period was prolonged and not quite consistent with the usual course of events. The physicians on the ward apparently did not suspect a complicating infection, but they did make the usual efforts to detect a bacteremia or a focus of infection. If the final episode had been caused by a bacterium, I presume it would have been identified. The blood culture was

never positive. The sputum culture contained *Staphylococcus,* which is not surprising and cannot necessarily be implicated as a cause of disease. One must then turn to some of the more unusual infections, and these are almost the rule in this institution.

We often see fungus infections developing in patients with neoplastic disease. Many times the patient has been infected with the fungus earlier, and, with the onset of the neoplastic disease and its treatment, relapse occurs. Thus, a patient who had had coccidioidomycosis could develop leukemia, erode an infected node, and once again develop active infection with the fungus. This has happened; it has also happened with histoplasmosis. Cryptococcosis complicates various kinds of neoplastic disease; however, in my experience it is more common in lymphosarcoma and Hodgkin's disease. Actinomycosis is not, I think, commonly associated with neoplastic disease, nor do I recall ever seeing blastomycosis in this situation. *Candida* often grows on mucous surfaces in sick people, but it rarely is the cause of serious illness.

We can never forget tuberculosis as a cause of disease in patients with neoplastic illness or something else. This has been forcibly brought home to us occasionally when we have least expected it. Of all the diseases that I have listed for you, any one could have been responsible, I believe, for the picture this man presented. However, I am not going to make a diagnosis of any of them.

Now let us turn briefly to some of the other aspects of this patient's illness. It is hard to discard the possibility that he did have thrombophlebitis. The description sounds like thrombophlebitis to me and, lacking any other evidence, I will make a diagnosis of thrombophlebitis of the left leg. I will say now, however, that I do not believe his terminal episode was a result of a large pulmonary embolization from this site.

What about the terminal episode? Obviously, the lungs were importantly concerned in it. The patient died a respiratory death without much evidence of cardiac disease. I do not think he had endocarditis. I was quite disturbed in the diagnosis that I made when I learned that the lung changes were so recent. I believe—if I am correct in my diagnosis—that the pulmonary disease had existed much longer than is suggested by the evidence now available to us. I would judge that the pulmonary disease I am going to implicate as a possible cause of this man's death must have existed for at least three or four weeks.

The diagnosis I want to introduce at this point is one which has been known to cause acute respiratory infection and functional failure. It seems to have some specific predilection for leukemics, enough so that, even though this diagnosis is totally wrong, at least I have literary substantiation for introducing it as an explanation for this man's illness.[2, 3] The disease I am thinking of is mucor, a fungus disease. It is widely distributed in nature, and thus may be easily accessible to patients with increased susceptibility to infections.

How does this disease give this picture? Mucor causes two kinds of death: by cerebral invasion, with large-scale destruction of the brain tissue and blood vessels of the brain; and then—pertinent to our discussion this afternoon—it may have a respiratory route of invasion. It may invade the arteries and veins of the lung rather selectively, so that the focus of the infection is in the pulmonary blood vessels. It actually penetrates the walls of the arteries of the

lung and causes huge gray thromboses, consisting of mixtures of blood clot and fungus, with consequent mechanical obstruction. It may propagate upstream to cause complete pulmonary artery obstruction.

What is my basis for introducing this diagnosis in the present case? Of the approximately two dozen cases of mucor infection of the lung that have been reported, a large number have occurred in patients with leukemia, and their protocols are not far different from this one.

None had thrombophlebitis, and most had the roentgenographic changes in the lung lasting longer than the changes in this patient, but death was sometimes sudden, as in this case. There may be some degree of dissemination of the fungus to other organs—spleen, liver and kidney—but it is much less marked than the pulmonary involvement. Thus, it is my opinion this patient died of mucor infection of the lung which complicated the terminal stage of leukemia.

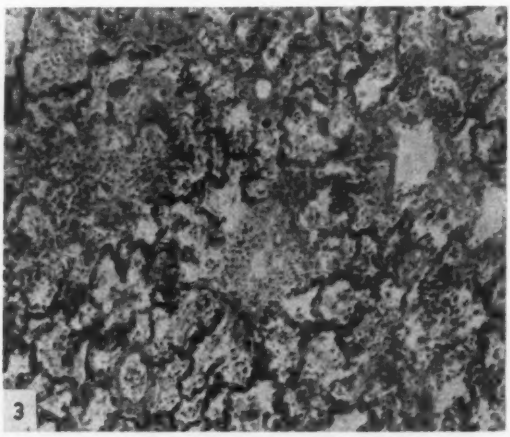

FIG. 3. Lung. The alveoli contain bloody fluid. Very large cells are present in several alveoli. (CC-NIH Aut. No. A58-252.) H. and E. 67 ×.

DR. CHARLES G. ZUBROD: Thank you, Dr. Knight.

Dr. John Edgcomb, of the Pathologic Anatomy Branch, National Cancer Institute, will present the autopsy findings.

DR. JOHN EDGCOMB: I think it is not possible to make the diagnosis from the data presented.

At necropsy the body was 5 feet 10 inches long, and weighed 145 pounds. The left leg was greatly swollen. Although attempts were made, no clots were expressed from the veins of either leg. There was bilateral fibrinous pleuritis in the thorax. The pericardial sac contained 200 c.c. of serous fluid, and there was fibrous and fibrinous pericarditis. The pulmonary arteries contained some soft red clots which had the form of the vessels containing them. Two microscopic sections of the clots are indistinguishable from postmortem thrombi. The left lung weighed 800 gm., and the right lung weighed 1,100 gm. Both were mottled blue and red. Small indistinct peribronchial nodules were palpable in each lung.

The liver and spleen each weighed 2,300 gm. Red and white infarcts were present in the spleen. There was a small ulcer in the upper third of the esophagus.

The diagnoses written on the certificate of death were myelocytic leukemia and bronchopneumonia. The diagnosis of myelocytic leukemia was repeatedly confirmed by microscopic examination. Hemorrhagic leukemic infiltrates were present in the lymph nodes, bone marrow, spleen, liver, kidneys, lungs, epicardium, urinary bladder, pancreas and brain.

Some of the pulmonary foci thought to represent bronchopneumonia were hemorrhagic, and contained variable numbers of immature and mature myelocytes. In some alveoli there were enlarged cells, the nuclei of which con-

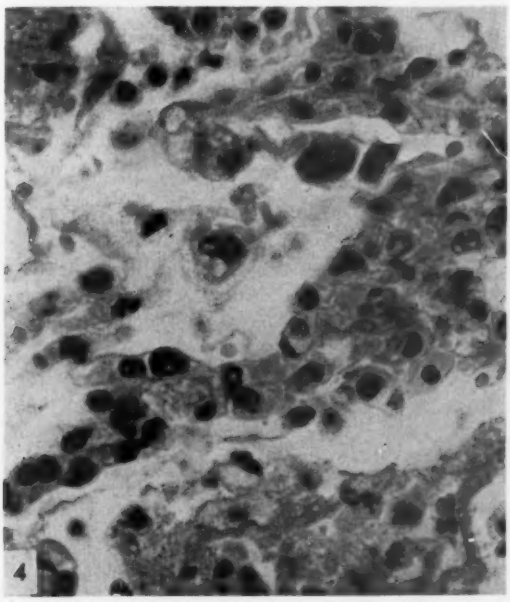

FIG. 4. Lung. Cytomegaly of several cells in an alveolus. In the nucleus of one cell there is an inclusion characteristic of cytomegalic inclusion disease. (CC-NIH Aut. No. A58-252.) H. and E. 510×.

tained hemotoxyphilic inclusions (figures 3 and 4). Similar cells, characteristic of cytomegalic inclusion disease, were present in the epithelium of the prostatic ducts (figures 5 and 6), the sinusoids of the spleen (figure 7), the endothelium of veins at the base of the esophageal ulcer (figure 8), the epithelium of pancreatic ducts, urinary bladder, and renal tubules, and the adrenal medullae.

In necropsy material at the Clinical Center, cytomegalic inclusion disease has been seen in six adults and in one child. Of the adults, two had Hodgkin's disease, one agnogenic myeloid metaplasia, one myelocytic leukemia, one mycosis fungoides, and one agammaglobulinemia. The child had lymphocytic

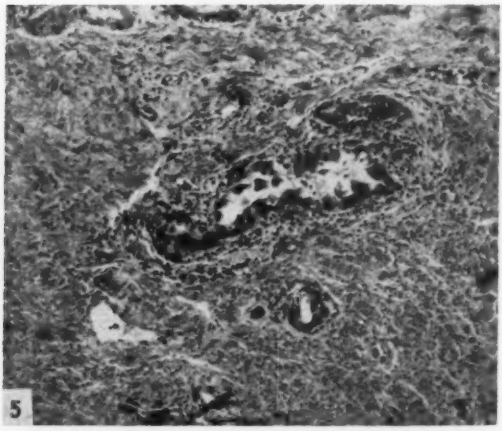

FIG. 5. Prostate gland. Cytomegaly of the ductal epithelium. (CC-NIH Aut. No. A58-252.) H. and E. 85×.

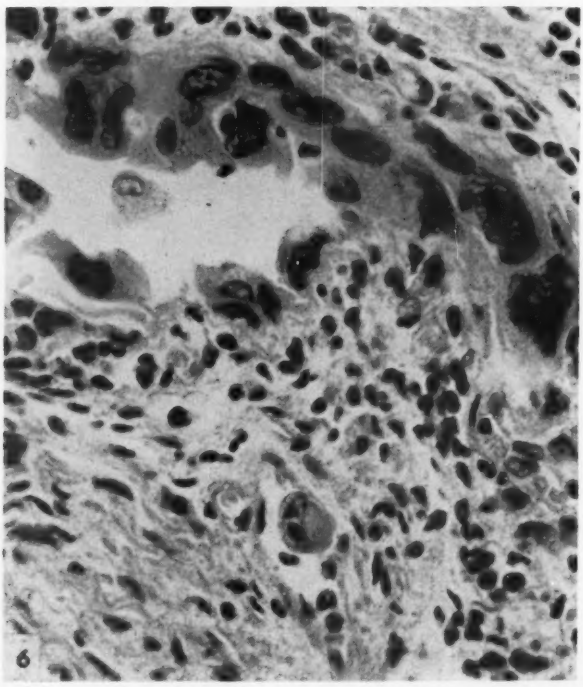

FIG. 6. Prostate gland. Cytomegaly and inclusion in the ductal epithelium of the prostate gland. One cytomegalic cell in the lower portion of the photograph may be situated in the endothelium of a small vein. (CC-NIH Aut. No. A58-252.) H. and E. 510×.

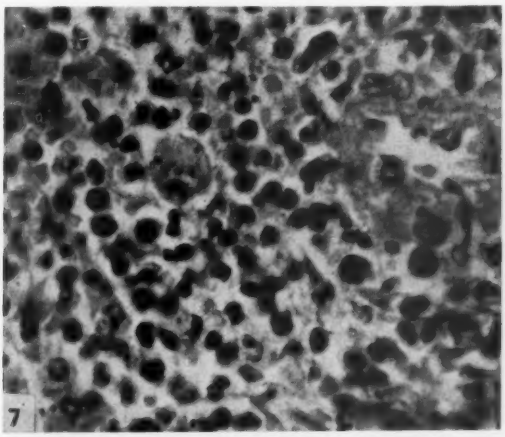

FIG. 7. Spleen. Cytomegalic cell among leukemic cells. (CC-NIH Aut. No. A58-252.) H. and E. 590×.

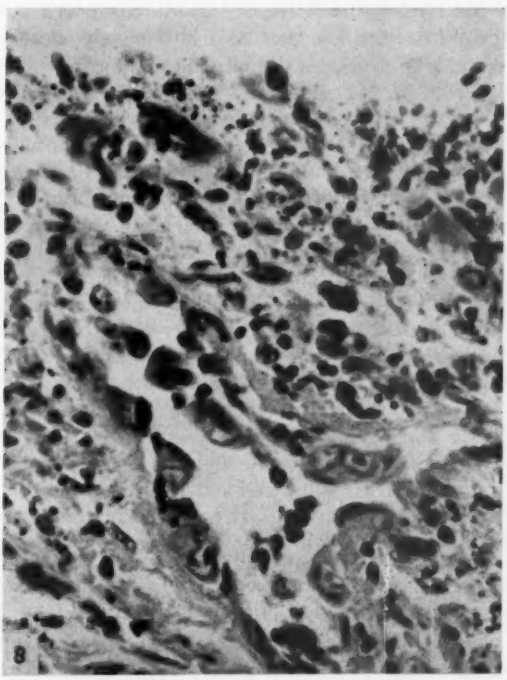

FIG. 8. Ulcer, esophagus. Cytomegaly and inclusions in the endothelium of a vein. (CC-NIH Aut. No. A58-252.) H. and E. 510×.

leukemia. In Munich in 1904, Jesionek and Kiolemenoglou published the first illustration of the then unrecognized cytomegalic inclusion disease as part of a description of protozoan-like forms found in a fetus.[4] In 1921 Goodpasture and Talbot implied that the disease might be caused by a virus.[6] In 1925, von Glahn and Pappenheimer first recognized the disease in an adult at necropsy.[5]

DR. CHARLES G. ZUBROD: Thank you, Dr. Edgcomb.

I should like to call on Dr. Wallace P. Rowe, head of the Oncolytic and Oncogenic Virus Unit in the Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, to tell us more about cytomegalic inclusion disease.

DR. WALLACE P. ROWE: Our laboratory has been working with the salivary gland or cytomegalic disease virus for several years, with particular interest in its epidemiology and in the evaluation of diagnostic tests.

As Dr. Edgcomb pointed out, this virus has been known to pathologists for some 55 years, but only in the past seven years has a laboratory system been available for virologic study. In 1953, Dr. Margaret Smith showed that the virus would multiply in tissue cultures of human fibroblasts, with production of a characteristic cytopathic effect. Since that time, many strains of the virus have been isolated, but the agent represents one of the most difficult viruses to work with that the virologist will encounter—the agent is not well adapted to tissue culture, grows to very low titer, and is relatively unstable.

We have been able to develop a complement-fixation test for the virus which is reliable and sensitive, and we have used this in conjunction with tissue culture isolation tests to study the epidemiology of the infection. These studies indicate that infection is widespread. In surveys of normal individuals in many parts of the world it has been found that many children and the great majority of adults have complement-fixing and/or neutralizing antibody.

Although the virus is widespread, infection has been associated etiologically with only a few types of clinical disease. Cytomegalic inclusion disease of the newborn is now a well defined clinical entity, caused by prenatal or neonatal infection with the virus. Also, the virus may produce secondary infections in children or adults debilitated by a primary disease. However, the great majority of infections apparently are completely subclinical. We have directed most of our attention to the subclinical infections for the purpose of determining the frequency and duration of virus excretion.

Among children seven months to four years of age from the Washington, D. C., lower economic groups, approximately 10 to 15% possess complement-fixing antibody for the virus, and virus can be recovered from the saliva and the urine of about half of the antibody-positive children at any single time period. In contrast, children without complement-fixing antibody have been uniformly negative for virus. The infection is not only prevalent but is also chronic; in serial tests on the same antibody-positive children, virus has been recovered from saliva and urine over periods of eight months or more, and as long as several years after the child had been known to be positive for antibody. An unusual finding is that occasionally a child demonstrated continued excretion of virus, but the complement-fixing antibody titer progressively declined and even became negative. These results indicate that from 5 to 8% of apparently

normal infants are actively and chronically infected with the virus, and are potential sources of infection. Virus has not, however, been recovered from the saliva of adults.

We have been fortunate in obtaining serum from several of the adult cases where Dr. Edgcomb found inclusion bodies, and this provided an opportunity to evaluate the complement-fixation test in terms of these adult secondary infections. In the case presented today, P. P., there were available seven sera taken during the period from 15 months until four days before death, the last serum being taken at the time of the temperature spike. In none of the sera was there any complement-fixing or neutralizing antibody to our Ad. 169 strain of SGV. In contrast, other patients showed different patterns. Patient J. P., who had disseminated disease at autopsy, had low titer antibody in serum taken three months before death. Patient E. R., with a localized lesion in the pancreas, had a high titer of antibody in serum taken one month before death. Case D. R., with a localized lesion in the adrenal, had a minimal titer seven months before death, and the same titer in a serum taken one week before death.

Thus the complement-fixation test seems to be totally without value for diagnosis of secondary infection. However, we do not know whether these infections may have represented terminal dissemination of virus, with insufficient time for an antigenic response. Also, the problem of multiple serologic types of cytomegalic disease virus must be considered. Dr. Thomas Weller, of Harvard University, has recently described distinct serologic differences between strains as determined by neutralizing antibody responses. Whether the complement-fixation test will show group or type specificity remains to be determined.

The source of the infection in these hospital cases is an important one from the epidemiologic and control points of view. The possibility that the virus has been present in the patients' salivary glands since childhood must be considered, in view of the long persistence of salivary gland viruses in laboratory animal systems. It is conceivable that the virus could be activated by the various steroid, antimetabolite or radiation treatments. However, in humans there is no direct evidence bearing on this point. Since a considerable number of children are excreting virus in the saliva and urine, the possibility must be considered that contact with children on hospital wards was a source of infection. One mechanism which probably should be considered is blood transfusions. Although virus has never been demonstrated in blood, it is possible that the virus could be there in small amounts, since the tests for virus are so insensitive that a viremia could hardly be detected.

I would like to make one final comment on the rarity of this infection. Only 18 cases or so in adults are reported in the literature, but it is quite significant that within three years Dr. Edgcomb has encountered one third of the entire world output of the last 50 years. Also, in the last eight years we have been trying to find clinical cases of cytomegalic disease in infants in the Washington area, without success until last year when, within a period of a single year, four cases were brought to our attention. I do not think these two findings mean that we are encountering an epidemic of cytomegalic virus, but rather that our pathologists and clinicians are becoming more aware of it, and that we should expect to encounter this disease much more often in the future.

DR. CHARLES G. ZUBROD: Thank you, Dr. Rowe.

Are there any questions or comments?

DR. T. F. HILBISH: Yes. My understanding is that cytomegalic inclusion disease is seen concomitantly with terminal states, or debilitated states, and I wonder whether the work that has been done here and elsewhere can prove that this is a happenstance, or whether this is really and truly a significant infection.

DR. JOHN EDGCOMB: I have seen two patients who died with acute respiratory disease: the patient whose course has been presented here, and a woman who died with bilateral pleural effusions and mycosis fungoides. It is not certain what signs and symptoms in adults can be attributed to cytomegalic inclusion disease. It is not known whether pulmonary lesions may develop either as a result of viremia or from the aspiration of infected saliva.

Question: In view of the fact that several adult cases have been patients with myelocytic leukemia, I wonder if attempts at tissue culture in comparable tissues have been made in leukemic tissue culture.

DR. WALLACE P. ROWE: I know of no studies in tissue-cultured leukemic cells. As far as is known, the virus grows in tissue cultures only in fibroblasts, in very marked contrast to its behavior in the living organism, where it is primarily epitheliotropic.

Question: Were any of these inclusions seen in the leukemic cells in this tissue?

DR. JOHN EDGCOMB: No.

SUMMARIO IN INTERLINGUA

Es presentate le caso de un patiente mascule de 37 annos de etate qui suffreva de chronic leucemia granulocytic e qui moriva brevemente post un morbo febril characterisate per un infiltration diffuse e propagative del pulmon. Le examine necroptic revelava, a parte le leucemia granulocytic, un extense infection per le virus de morbo de inclusion cytomegalic, le qual habeva afficite le pulmones, le prostata, le splen, le esophago, le pancreas, le vesica, le renes, e le adrenales. Al Centro Clinic, morbo de inclusion cytomegalic ha essite constatate in le necropsias de sex adultos e un patiente pediatric. Le morbos primari in iste casos esseva morbo de Hodgkin, metaplasia myeloide, leucemia myelocytic, mycosis fungoide, leucemia lymphocytic, e agammaglobulinemia. Ben que infectiones per iste virus es commun in neonatos, solmente 18 casos es cognoscite in que le victimas de tales esseva adultos. Recente disveloppamentos de technica laboratorial in le dominio de studios de morbo de inclusion cytomegalic ha resultate in le demonstration que iste infectiones es commun, subclinic, e frequentemente chronic. Inter 5 e 8% del infantes neonate ha le virus in lor saliva. Le studio del seros del patientes discutite in le presente reporto revelava nulle correlation inter le titro de anticorpore de fixation de complemento e le grado del infection clinic. Nove technicas e le recognition recente que le virus existe in plure racias va possibilemente render possibile le characterisation del epidemiologia de iste morbo virusal.

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CASE REPORTS

AN ANAPHYLACTIC REACTION TO SODIUM DEHYDROCHOLATE (DECHOLIN)*

By JOHN P. ELLIOTT, JR., M.D., RANSOM VIDRINE, M.D., and ALLAN M. GOLDMAN, M.D., F.A.C.P, *New Orleans, Louisiana*

DECHOLIN is a sodium salt of dehydrocholic acid, an oxidative product of cholic acid, which is derived from the natural bile salts.

Since Winternitz introduced the use of Decholin in the measurement of circulation time in 1931, its usefulness has been both substantial and well documented.[10, 5, 9] It is recommended not only for determination of circulation time, but for treatment of penicillin reactions, as a diuretic, and for its hydrochlororetic action in cholangitis and postoperative cholecystectomies.

It is considered to be the least toxic of all the bile salts in man,[1, 12] although a 2% solution will stop the heart of a rabbit within a few seconds.[1] Allergic reactions to this drug are rare, if the literature reflects a true picture of the incidence of allergy. Only two cases of anaphylaxis are reported in the American literature. The following is a report of anaphylaxis to Decholin to add to this list.

CASE REPORT

A 71 year old white male was admitted to the Urology Service of Touro Infirmary on September 14, 1959, with a chief complaint of urinary frequency, urgency, and incontinence which had become progressively worse over the last 30 days. A urologic examination revealed an enlarged prostate. *Escherichia coli* was cultured from the urine; it was sensitive to all drugs tested.

The electrocardiogram was reported within normal limits. There was history of a recent diagnosis of early glaucoma.

On September 29, 1959, a suprapubic prostatectomy was done without difficulty. The pathologic report showed benign prostatic hypertrophy with a focal, well differentiated carcinoma.

On the tenth postoperative day a moderate peripheral edema was noted and the patient was given a diuretic. A repeat electrocardiogram at this time was again normal. There were no signs of congestive heart failure. A resistant Pseudomonas organism was cultured from the urine. The blood urea nitrogen had risen to 20 mg.%.

The patient was scheduled for a bilateral orchiectomy. After preoperative medication with Demerol, 100 mg., and atropine, gr. 1/150, he was noted, in the operating room, to be cold and sweaty. Blood pressure was 70/50 mm. of Hg. An electrocardiogram done at this time was not diagnostic; however, serial electrocardiograms

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and SGO-T determinations gave support to a myocardial infarction. One injection of a vasopressor agent was given, and the patient was started on oxygen and an anticoagulant, heparin, LH400. That afternoon the question of cardiac decompensation arose because of the evident edema and moderate dyspnea. A venous pressure and a circulation time were done. The venous pressure was found to be within normal limits. A standard solution of 20% Decholin was used for the circulation time, which was 23 seconds. Within 30 to 40 seconds after this injection the patient coughed and suddenly gave a loud, inspiratory, high-pitched gasp. Concomitantly his entire body became rigid, and laryngeal spasm was evidenced by a completely obstructed airway and a violent heaving of the abdominal muscles. There was a vigorous, shaking convulsion, during which the patient had to be held in bed. Immediately, 1 c.c. of 1:1000 adrenalin was injected. Following the injection the patient suddenly became flaccid, and began to breathe noisily and to cough. His lungs were filled with fluid, and copious quantities of clear, watery mucus were expectorated. He was very weak, and completely amnesic regarding the details of the episode. Total duration of the reaction was approximately two minutes.

Within several hours the patient's blood pressure slowly declined, and he was maintained on intravenous Aramine for two days. Partial renal shutdown further complicated his course, as evidenced by a urinary volume of less than 500 c.c. daily, and an elevation of the blood urea nitrogen to 76 mg.% and of the serum potassium to 5.5 mg.%. On the fifth postinfarct day he had a diuresis, and subsequently did well and was discharged on November 18, 1959.

Follow-up two months later showed no change in his status.

Review and Discussion

In 1944 Leys [4] reported three cases of reaction to Decholin, one of whom died. He concluded: "Despite the usefulness of the test, its seems inadvisable to use it so long as this possibility exists."

In the same year Winternitz, who had introduced the use of Decholin in 1931, answered this report.[2] He commented that Winkler and Bucharest had reported a few cases of collapse and fluctuations of blood pressure and pulse associated with intravenous Decholin. His own experience covered about 2,000 injections, with three instances of nonfatal collapse, "which is the number one would expect after speed injection of any anisotonic and anisomotic solution, particularly in collapsed patients and patients with terminal heart failure in which the method has been extensively used. Other adverse effects include nausea and vomiting that we have seen in a few sensitive people."

Winternitz goes on to say, however, that "personally I have almost abandoned the method in favor of the calcium method in which 5 c.c. of twenty per cent calcium gluconate is used."

The following tabulation at top of next page is a summary of reported Decholin reactions in the American literature.

Since the drug is widely used, there must certainly be a number of unreported cases.

Norman's [5] case of anaphylactic shock had had intravenous Decholin one week prior to the second injection. A subsequent skin test was positive. He concluded that a patient can be sensitized to Decholin.

Coggins et al.[6] concluded that, "in patients with an allergy history, Decholin should be abandoned in favor of calcium gluconate."

Author	Age	Sex	Type of Reaction	Allergic History	Remarks
Norman[5]	75	M	Anaphylactoid	Negative	Prompt response to a vasopressor agent
	42	M	Asthma	Negative	Responded to epinephrine
	64	M	Urticaria	Negative	Responded to antihistamines
Suckle[8]	52	M	Urticaria and mild asthmatic symptoms	Negative	Responded to epinephrine and antihistamines
Coggins[6]	64	F	Circulatory collapse	Negative	Delayed response to efforts to support circulation
Elliott et al. (present case)	71	M	Anaphylactoid	Negative	Responded to epinephrine

Suckle[8] theorized as to the mechanism: "The simple chemical substance per se is incapable of acting as an antigen, but in combination with body substances, particularly proteins, it becomes a perfect antigen capable of producing allergic manifestations."

Decholin has been used with good results in the treatment of delayed serum-sickness type of penicillin reactions.[12] Injections are given slowly for this use. No reactions are reported in the literature; however, the above three authors encourage cautiousness with its use in patients with an allergic history.

What other substances are available for use in circulation time determinations? Calcium gluconate has been mentioned above. The end point of both drugs is equally accurate, either one having a subjective end point and being therefore subject to some error. Bower and Mengle,[3] however, report two deaths due to the use of 10 c.c. and 5 c.c., respectively, of 5% intravenous calcium gluconate in patients on digitalis. The additive effect of these two drugs is well known. To the authors, the routine use of this drug in the measurement of circulation time is fraught with danger.

Vitamins have been used in this test as a measure of end point. Armanino and Scott[7] report a case of anaphylaxis to thiamine, with subsequent death of the patient, and their bibliography contains six other reports covering a three-year period. Their case had had prior sensitization with thiamine injections, and had had a mild reaction to one of them.

Conclusions

Measurement of circulation time has become a routine procedure with venous pressure measurement in many clinics. The authors feel that it should be used only when the clinical evaluation and direct measurement of venous pressure are not expected to give the necessary information. Though reactions to the drugs used parenterally for determining circulation time are infrequent, they do occur and may be severe or even fatal.

Serious reactions to parenteral Decholin can occur without any previous history of allergy. Patients can also be sensitized to Decholin.

Routine use of calcium gluconate for determination of circulation time is not recommended, since fatal reactions have been reported. Serious reactions to parenteral thiamine used for this purpose have also occurred.

Summary

A case is reported of an anaphylactic reaction to Decholin, bringing the cases already reported in the American literature to three. A review of the literature is given.

Summario in Interlingua

Un masculo de racia blanc de 71 annos de etate disveloppava signos de disfallimento circulatori post un operation pro carcinoma del prostata. Un determination del tempore de circulation esseva tentate con le uso de un solution standard de 20% de Decholina.

Intra trenta a quaranta secundas post le injection, le patiente tussiva e ejaculava un forte e altisonante ruito respiratori. Concomitantemente su integre corpore deveniva rigide. Spasmos laryngee deveniva evidente per le occurrentia de un complete obstruction del vias aeree e un violente labor del musculos abdominal. Sequeva un vigorose convulsion agitative. Un centimetro cubic de adrenalina esseva injicite immediatemente. Promptemente le patiente deveniva flaccide, e ille comenciava respirar ruitosemente e etiam tussiva. Grande quantitates de un clar e aquose muco esseva expectorate. Le patiente esseva extrememente debile e exprimeva un complete amnesia con respecto a ille episodio que durava approximativemente duo minutas. Le tension de sanguine declinava gradualmente, e il esseva necessari usar Aramina per via intravenose durante duo dies. Clausura renal complicava le curso additionalmente, sed post cinque dies ille effectuava un diurese. Ille continuava meliorar se e esseva dimittite ab le hospital le 18 de novembre 1959 ubi ille habeva arrivate le 29 de septembre.

Duo altere casos de un typo anaphylactic de reaction a Decholina se trova reportate in le litteratura american. Un numero de leve responsas allergic es etiam mentionate.

Altere substantias—per exemplo gluconato de calcium—pote esser usate pro mesurar le puncto terminal del tempore circulatori, sed le disastrose consequentias in patientes sub therapia a digitalis es ben cognoscite. Vitaminas per via intravenose ha etiam essite usate, sed anaphylaxe con exito mortal ha occurrite e se trova reportate in le litteratura. Isto es specialmente ver in le caso de patientes con un historia allergic.

Mesurationes del tension venose e del tempore de circulation ha devenite un procedimento routinari. Reactiones post Decholina usate pro determinar le tempore circulatori pote occurrer sin ulle previe historia de allergia. In le opinion del autores, Decholina deberea esser usate solmente quando le evalutation clinic del condition e directe mesurationes del tension venose non provide omne le requirite information.

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BOECK'S SARCOIDOSIS SIMULATING HYPERPARATHYROIDISM *

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That Boeck's sarcoidosis could be mistaken for hyperparathyroidism was pointed out by Albright and Reifenstein [1] several years ago. They noted that bone changes, high serum alkaline phosphatase levels, hypercalcemia, hypercalciuria, and kidney stones might be found in both diseases. It was subsequently shown that a negative calcium balance, characteristically found in primary hyperparathyroidism, is also present in sarcoidosis with hypercalcemia.[2] Since these initial studies, several case reports have appeared illustrating the similarities that exist in these two conditions, as well as the difficulties that may arise in attempting to distinguish between them.[3, 4, 5, 6, 7, 8] In most of these cases, however, the correct diagnosis was suggested either by the history, physical examination, laboratory determinations, special studies, or a combination of these procedures. Where sarcoidosis was etiologically related to hypercalcemia, one or more of the various stigmata that accompany this disease were present.

We have recently encountered a case presenting with hypercalcemia, nephrolithiasis, and renal failure, in which complete study of the patient seemed to eliminate all diagnostic considerations except hyperparathyroidism. The correct diagnosis of Boeck's sarcoidosis was made only at the time of surgical exploration of the neck in search of a parathyroid adenoma or hyperplasia. At that time, two lymph nodes were removed which were histologically characteristic of sarcoidosis. Review of the American literature has failed to reveal a similar case of Boeck's sarcoidosis with hypercalcemia, nephrolithiasis and renal failure in which thorough study did not suggest the underlying disease. The case is presented below to emphasize the importance of considering this condition in all cases of hypercalcemia, with or without renal involvement, when the etiology is not clear.

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Case Report

A 46 year old white male was transferred to Temple University Medical Center on February 21, 1959, from another hospital where the findings of hypercalcemia and nephrocalcinosis had been noted. The patient had apparently been in good health until June, 1958, at which time symptoms of weight loss, weakness, and malaise appeared. By November, 1958, he had lost 47 pounds of weight and was complaining of dizziness and staggering gait, both of which interfered with his occupation of masonry. At this time he also noted pain in many joints of the upper and lower extremities, not associated with inflammatory signs or systemic symptoms. He had initially been hospitalized in December, 1958. The dizziness, ataxia, and joint symptoms began to subside spontaneously shortly after admission. However, findings of elevated serum calcium and phosphorus, nephrocalcinosis, azotemia, and diminished renal function were noted, and he was transferred to Temple University Medical Center with the diagnosis of possible hyperparathyroidism.

Physical examination at that time revealed calcium deposition in the cornea and conjunctiva. There was no lymphadenopathy, and no abnormal masses were present in the neck. Mild pulmonary emphysema was evident. The lungs were clear to percussion and auscultation. Findings on examination of the cardiovascular system were not remarkable. No hepatosplenomegaly or skin lesions were present, and the neurologic examination was within normal limits.

X-rays of the long bones and hands revealed no evidence of demineralization, cystic change, or other abnormalities. X-rays of the neck showed calcification of a tracheal ring, with no evidence of a calcified parathyroid adenoma. A roentgenogram of the chest was normal except for soft tissue calcification outside of the lung fields. The lamina dura was present in all teeth. On retrograde pyelography bilateral nephrocalcinosis was revealed.

Laboratory studies were as follows: serum calcium, 14.3 mg.%; serum phosphorus, 4.7 mg.%; blood urea nitrogen, 51 mg.%; serum alkaline phosphatase, 9.9 King-Armstrong units; serum sodium, 138 mEq./L.; serum potassium, 4.8 mEq./L.; serum chloride, 103 mEq./L.; serum carbon dioxide content, 26 mEq./L.; hemoglobin, 11 gm.%; white blood cell count, 7,900 per cubic millimeter, with 76% polymorphonuclears, 11% lymphocytes, 10% monocytes, 2% eosinophils and 1% basophils; serum protein, 5.8 gm.%, with 4.1 gm.% albumin and 1.7 gm.% globulin; serum uric acid, 9.7 mg.%; erythrocyte sedimentation rate, 30 mm./60 minutes (Wintrobe). There was 1.1% excretion of phenolsulfonphthalein dye in 60 minutes. The urine concentration of the third specimen in Mosenthal's test was 1.010.

While in the hospital, the patient passed three stones from the urethra, all composed of calcium oxalate. He was placed on a diet restricted to 150 to 250 mg. of calcium daily for two and one-half weeks. At the end of that time, 24-hour urinary calcium excretions on each of five different days were 396, 460, 519, 506 and 507 mg. These values represented a negative calcium balance of greater than 146, 215, 269, 256 and 257 mg., respectively. The patient was then placed on a restricted phosphorus diet of 250 mg. daily for two weeks, after which there was no change in either serum calcium or phosphorus levels. Surgical exploration of the neck was subsequently carried out and three parathyroid glands were identified, all normal in appearance. One of these glands was removed, as were two lymph nodes from the inferior aspect of the thyroid gland. Histologically, the parathyroid gland was normal (figure 1). Both lymph nodes showed noncaseating granulomas, characteristic of sarcoidosis (figure 2). Liver biopsy and bone marrow aspirate examinations carried out after operation were normal histologically. The patient was discharged on prednisone, 40 mg. daily, in an attempt to reduce the serum calcium level, eliminate hypercalcuria, and improve renal function.

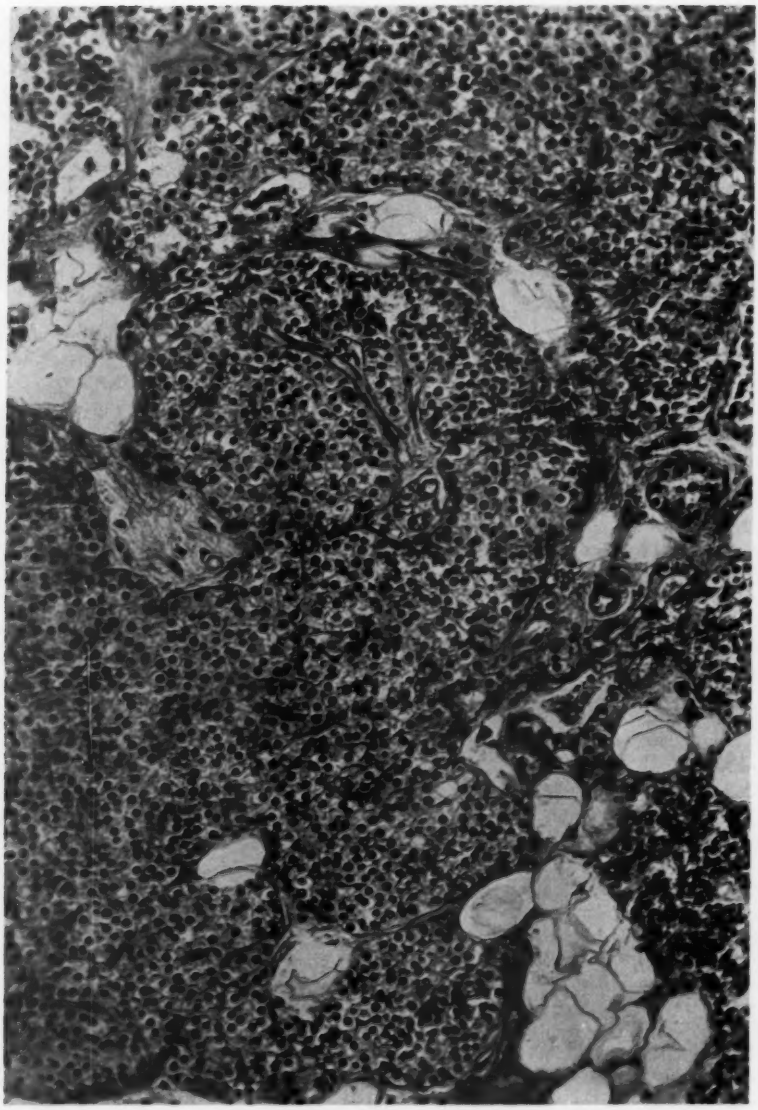

FIG. 1. Photomicrograph showing histologically normal parathyroid gland.

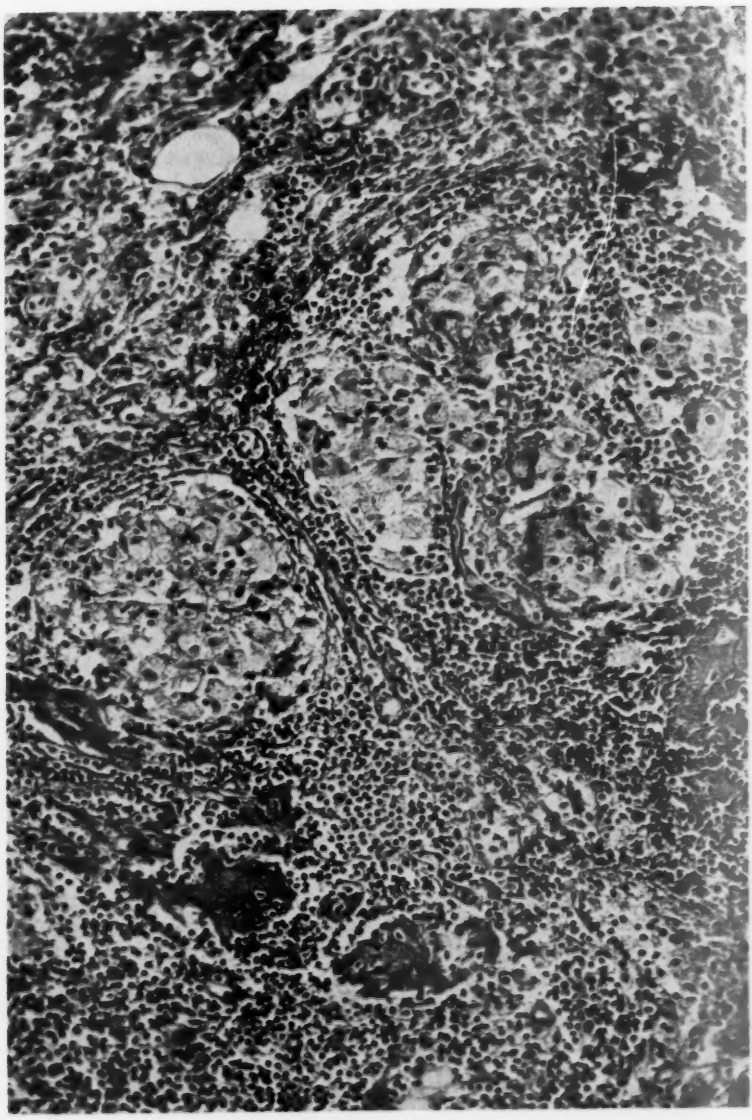

FIG. 2. Photomicrograph of lymph node, showing noncaseating granuloma characteristic of sarcoidosis.

Discussion

This case illustrates the importance of considering Boeck's sarcoidosis in the differential diagnosis of hypercalcemia with renal involvement. It also demonstrates the difficulties in differentiating this condition from hyperparathyroidism. Prior to surgical exploration, it appeared to us that primary hyperparathyroidism was the most likely diagnosis. Hyperplasia of the parathyroid glands subsequent to chronic renal disease with renal failure was also considered.

The patient's symptoms of weight loss, weakness, and malaise are common in hypercalcemia due to any cause.[9] Black [10] has noted disturbances in gait in persons with high serum calcium levels, a finding observed in the above case. It may be that the dizziness encountered here was also related to this chemical disturbance. Joint pains have been mentioned in association with sarcoidosis by Longcope and Freiman [11] as an infrequent manifestation. However, as an isolated symptom which did not persist, it was hardly suggestive of that disease in this patient.

The findings of conjunctival and corneal calcification, renal lithiasis, nephrocalcinosis, and metastatic soft tissue calcification are certainly the products of hypercalcemia per se. Renal insufficiency, too, is almost surely a result of the increase in serum calcium, with its subsequent deposition in the kidneys, and is amply evidenced by azotemia, hyperuricemia, profoundly diminished excretion of phenolsulfonphthalein dye, and the inability to concentrate the urine. The high normal values for serum phosphorus seen here, ordinarily a point against primary hyperparathyroidism, are of no diagnostic aid in the presence of severe renal disease, which frequently restricts the excretion of phosphorus and results in elevation of the serum levels. Renal function in such cases is so poor that the interpretation of most of the tests of parathyroid function is seldom possible.

The absence of x-ray changes involving the bones lends no support to either diagnosis, since both diseases may present in this manner, even when alterations in the serum calcium exist. The observation that the lamina dura was present is not helpful in excluding hyperparathyroidism, because this disease often occurs without bony changes. Other aids in the diagnosis of sarcoidosis not found in this case were hepatosplenomegaly, lymphadenopathy, skin lesions, suggestive eye changes, hyperglobinemia,[6] liver and bone marrow involvement, pulmonary changes on x-ray, and fever.

It has been noted that in sarcoidosis the serum calcium will usually fall upon administration of cortisone,[13] whereas in hyperparathyroidism cortisone produces no change in the serum calcium level. This difference of response to cortisone in the two conditions may be a worthwhile way of differentiating them.

The explanation of the negative calcium balance seen in sarcoidosis has not been established. It has been definitely shown that the intestinal absorption of calcium is increased above normal in this disease. However, urinary excretion is greater than can be accounted for by increased absorption alone.[2] Bone may be the source of this additional calcium, since Schaumann [12] demonstrated histologically that granulomatous involvement of bone may occur in sarcoidosis without visible x-ray changes. Others have suggested that the hypercalciuria seen in this condition is due to endogenous hypervitaminosis D.[2]

Summary

A case of Boeck's sarcoidosis with hypercalcemia, nephrolithiasis, renal insufficiency, a negative calcium balance, and no other manifestations of the underlying disease, is presented to illustrate the difficulty in diagnosing this condition and distinguishing it from hyperparathyroidism. The correct diagnosis in this case was made in an incidental manner during a surgical procedure intended to prove the preoperative diagnosis of parathyroid adenoma or hyperplasia. It would appear that certain cases of "idiopathic" nephrolithiasis and hypercalciuria may actually represent sarcoidosis, and should be investigated for that possibility. It is hoped, too, that cases of the above nature will stimulate further investigation of the pathophysiology of this disease leading to a better means of diagnosis.

Summario in Interlingua

Il existe plure reportos illustrante le similitudes de hyperparathyroidismo e sarcoidosis. Le constatationes que pote esser presente in ambe le morbos include hypercalciemia, elevate nivellos seral de phosphatase alcalin, calculos renal, e un negative balancia de calcium. Usualmente certes del aspectos specificamente characteristic de sarcoidosis es presente e servi a establir le differentiation inter illo e hyperparathyroidismo quando il se tracta de un sarcoidosis que se presenta primarimente como un defecto in le metabolismo de calcium.

Recentemente nos ha habite un caso in que le complete studio del patiente pareva excluder ab le consideration diagnostic omne possibilitates excepte hyperparathyroidismo. Le correcte diagnose—i.e. sarcoidosis—esseva recognoscite solmente al tempore del exploration chirurgic del collo visante al discoperta de un adenoma o hyperplasia parathyroidic sed resultante in le ablation de duo nodos lymphatic que esseva histologicamente characteristic de sarcoidosis. Le patiente esseva un masculo de 46 annos de etate con nephrocalcinosis bilateral. Esseva presente depositos de calcium in cornea e conjunctiva. Le roentgenogramma thoracic esseva normal con le exception de evidentia de calcification de tissu molle al extero del campos pulmonar. Le calcium seral esseva elevate a 14,3 mg%. Le phosphoro seral amontava a 4,7 mg%, le nitrogeno de urea sanguinee a 51 mg%. Studios reno-functional revelava marcate grados de dysfunction. Sub le conditiones de un restringite ingestion de calcium, mesurationes del calcium urinari revelava un negativitate del balancia de calcium amontante al media a 200 mg per die.

Le exploration chirurgic revelava normal glandulas parathyroidic, sed duo nodos lymphatic esseva excidite que revelava non-caseante granulomas typic de sarcoidosis.

Iste caso illustra le importantia de prender in consideration sarcoidosis de Boeck in le diagnose differential de hypercalciemia con affection del renes. Le explication del negative balancia de calcium in sarcoidosis es non ancora clar. Quando vitiation renal e azotemia es presente, le usual tests del function parathyroidic deveni van. Sub iste circumstantias, le differentiation del disordines deveni extrememente difficile. In un situation de iste genere, le uso de cortisona pote monstrar se de valor diagnostic. Il ha essite demonstrate que le elevate nivellos seral de calcium in sarcoidosis pote esser reducite per le administration de cortisona, durante que in hyperparathyroidismo le administration de cortisona exerce nulle effecto.

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IDIOPATHIC HYPOPARATHYROIDISM: REPORT OF A CASE WITH AUTOPSY FINDINGS*

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IDIOPATHIC hypoparathyroidism is uncommon. Steinberg and Waldron,[1] reviewing the literature in 1952, found only 52 cases satisfying their diagnostic criteria. Only four of these cases came to autopsy. On reviewing the literature since 1952, we have encountered reports of 56 additional cases,[2-35b] in three of which autopsies were done. A case presenting the clinical features of idiopathic hypoparathyroidism which terminated in death, and in which postmortem examination revealed the presence of a parathyroid gland, has recently been observed by us.

CASE REPORT

A 79 year old Italian-born, retired, widowed janitor was admitted to the Boston City Hospital on April 17, 1957, because of fever, rapid breathing and progressive unresponsiveness.

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The patient had previously been admitted to the Boston City Hospital on March 9, 1943, because of unconsciousness of several hours' duration. He had been asymptomatic until 10 days prior to the first admission, when he suddenly "stiffened" while lying in bed, "shook all over," and became unconscious for a few minutes. After this episode, slight weakness of the left arm and face was noted. A similar episode occurred three days later, and two more seizures occurred on the day of admission; following these latter episodes the patient failed to regain consciousness and was brought to the hospital. He regained consciousness shortly after admission. Physical examination revealed slight facial weakness on the left, and moderate weakness and spasticity of the left arm. Laboratory studies showed: blood hemoglobin concentration, 70% of normal; blood leukocyte count, 11,600 per cubic millimeter; serum nonprotein nitrogen concentration, 35 mg.%. Lumbar puncture revealed normal pressure of xanthochromic fluid, which contained 10 lymphocytes per cubic millimeter, and the spinal fluid protein concentration was 63 mg.%. Blood and spinal fluid Hinton tests were negative. The patient was discharged from the hospital five days after admission, and subsequently regained strength in the left arm and had no further seizures until four months prior to the second admission.

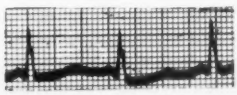
In 1946, complaints of failing vision led to the diagnosis of cataracts, but the patient was able to see well enough until December, 1956, when he required a guide, and at about this time became depressed and uncommunicative. Four months prior to the second admission he was treated by his physician at home for pneumonia. Shortly thereafter he began to suffer from recurrent seizures. These seizures, as described by the patient's family, were said to be preceded by periods of "nervousness," during which he displayed "twitches and tremors" and pulled at a handkerchief. He would then become "stiff all over," with tremor of arms and legs, the head being extended and the eyes directed upwards; there was foaming at the mouth, but no tongue-biting or incontinence. After such episodes, which lasted approximately 20 minutes, the patient was confused and weak for several hours. Seven such episodes occurred during the four-month period preceding admission, and in the three-week period prior to admission he suffered frequently from "twitches and tremors," became progressively weaker, and was confined to bed. Phenobarbital, prescribed by his physician to control the seizures, was discontinued because it produced somnolence. Cough productive of yellow sputum and associated with fever developed one week before admission. The patient then became dyspneic and progressively less responsive, and was admitted to the hospital. Physical examination revealed an elderly, unresponsive man breathing deeply and rapidly. The rectal temperature was 104° F.; pulse rhythm, regular at 130 per minute; respiratory rate, 32 per minute; blood pressure, 130/60 mm. Hg. The hair was grey and abundant. The skin was moist and warm. The pupils were 2 mm. in diameter and reacted briskly to light. The fundi were obscured by dense cataracts bilaterally, with crystal-shaped, needle-like formations in the lenses. The jaws were edentulous. The neck was supple, and there was no venous distention. The chest was emphysematous, and there was dullness on percussion over the right lung base. Diminished breath sounds and râles were noted over this region; a few râles were heard at the left base. There was no evidence of cardiac enlargement, and no murmurs were heard. The liver edge was palpable 2 cm. below the right costal margin in the midclavicular line. Large, irreducible scrotal hernias were present. The upper extremities and fingernails were normal. The feet were in plantar flexion because of bilateral shortening of the Achilles tendon, and the toes were in maximal plantar flexion. A black necrotic area, 2 by 2 cm., was noted over the left heel. The reflexes were hypoactive, and ankle jerks could not be elicited; the plantar responses were flexor.

Laboratory Studies: The hematocrit was 40%; leukocyte count, 19,250 per cubic millimeter. Analysis of a urine specimen obtained by catheter indicated: pH, 5.0;

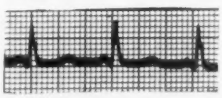
specific gravity, 1.020; albumin, 1 plus; reducing substances, acetone and bile, none. Urine sediment contained an occasional red blood cell, two to three white blood cells, and an occasional cast per high power field. Lumbar puncture revealed normal cerebrospinal fluid at a pressure of 170 mm. water. The stool was of normal color and consistency, without evidence of occult blood. Urine culture revealed *Candida albicans,* and sputum culture, hemolytic staphylococcus, *Escherichia coli* and *Bacillus pyocyaneus.*

Therapy consisting of intravenous fluids, penicillin and streptomycin was begun, and six hours later the patient was afebrile, although the respiratory rate was still rapid. The heart rate was 92, and the blood pressure, 100/60 mm. of Hg. An electrocardiogram at this time showed a greatly prolonged QT interval with a widened ST segment, suggesting hypocalcemia (figure 1). Serum electrolyte concentrations in a venous blood sample obtained at this time were: carbon dioxide content, 18.7

4-17 INITIAL E.C.G.
QT_C = 0.64 Ca = 5.0 P = 7.6



4-17 E.C.G. AFTER 2 GM. Ca GLUCONATE (I.V.)
QT_C = 0.53



4-20 TRACE OF Ca PRESENT IN URINE
QT_C = 0.48 Ca = 7.6 P = 3.9

FIG. 1. Electrocardiographic tracings (Lead 2). The upper tracing was obtained six hours after admission. The QT interval is prolonged by 0.15 sec. The middle tracing shows some reduction in the QT interval after administration of calcium gluconate. In the lower tracing, taken on the fourth hospital day, the QT interval is prolonged by 0.03 sec. The values of serum calcium and phosphorus (milligrams per 100 ml.) are those in blood samples obtained at the time of the corresponding tracings.

mEq./L.; chloride, 105 mEq./L.; sodium, 148 mEq./L.; potassium, 4.0 mEq./L.; calcium, 5.0 mg.%; inorganic phosphorus, 7.6 mg.%. The nonprotein nitrogen concentration was 40 mg.%, and the pH of venous blood, 7.26 to 7.36. Addition of Sulkowitch's reagent to urine produced no turbidity. Paper electrophoretic serum protein pattern showed a slight decrease in albumin and a moderate increase in alpha-2 globulin.

When the electrocardiographic suggestion of hypocalcemia was first observed, Chvostek's sign was elicited but Trousseau's sign was absent. Twenty cubic centimeters of 10% calcium gluconate solution given intravenously resulted in disappearance of Chvostek's sign and improvement in the electrocardiogram (figure 1).

On the second hospital day the patient was afebrile. The administration of calcium salts was continued, largely by vein, and, in addition, vitamin D_2 (50,000 units)

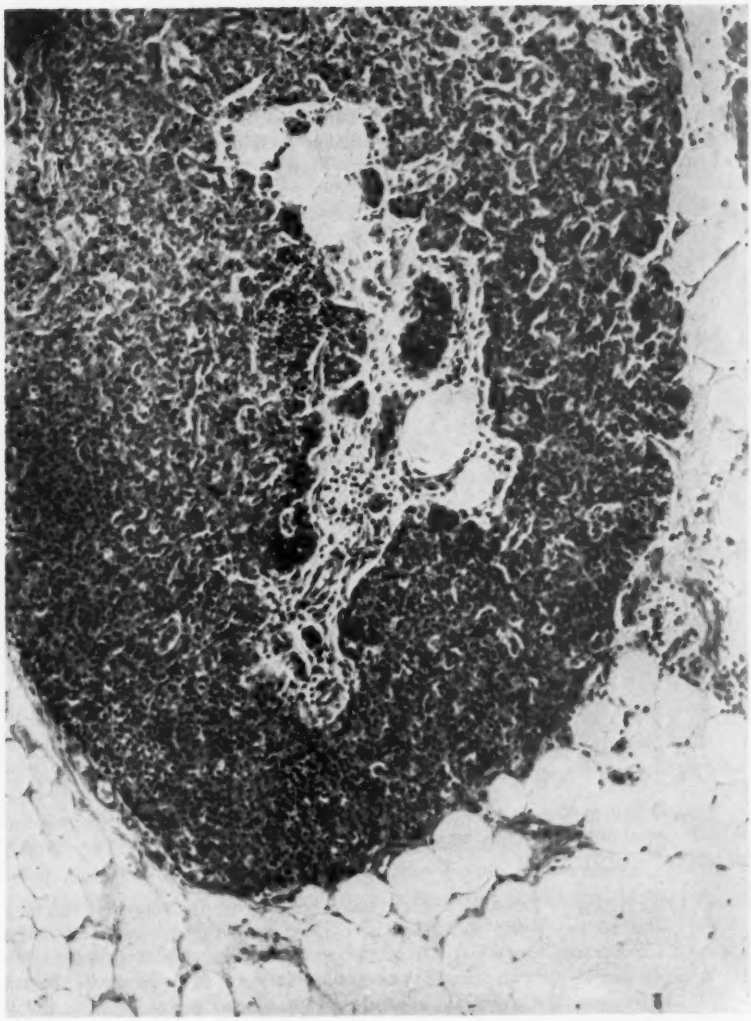


FIG. 2. Photomicrograph of parathyroid gland tissue from the reported case (140×).

was administered by stomach tube daily. By the third hospital day the patient's condition had improved sufficiently for him to be able to speak with his family for the first time. At this time the administration of 6.4 gm. of calcium lactate orally every four hours was begun, vitamin D was continued, and a milk-free diet was prescribed. Except for the development of a urinary tract infection the patient continued to improve until the fifth hospital day, when he became progressively more stuporous and finally unresponsive, the rectal temperature rose to 105° F., bilateral basal râles appeared, respiratory distress increased, and he died the following morning.

Roentgenogram of the chest taken on admission showed increased vascular markings, calcified hilar lymph nodes, and a calcified area at the left lung apex; there was no cardiac enlargement. Roentgenograms of the skull revealed vascular cal-

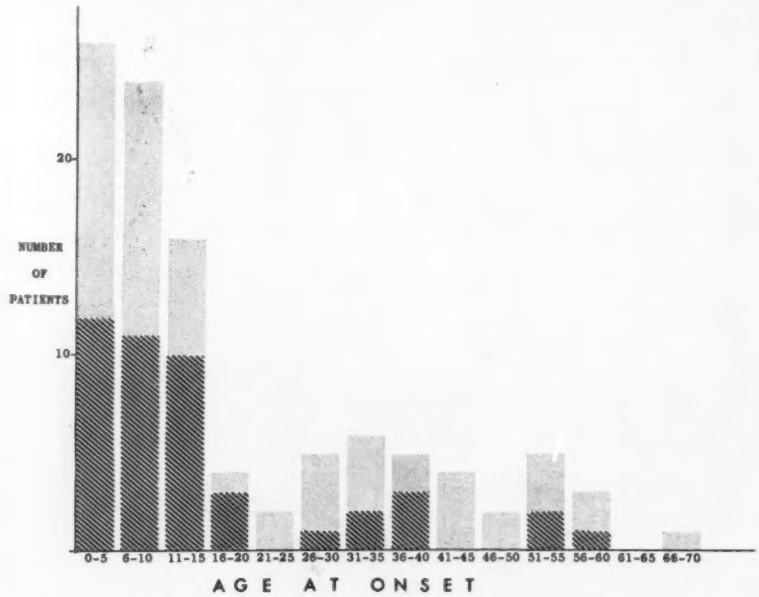


FIG. 3. Age distribution of idiopathic hypoparathyroidism. The hatched regions are the patients included in the report by Steinberg and Waldron.[1] The stippled areas are cases published since their report.

cifications in the region of the sella turcica, but there was no intracerebral calcification. X-ray films of the hands showed hypertrophic arthritic changes with slight decalcification. Repeated determinations of the serum concentrations of nonprotein nitrogen and electrolytes were as follows: nonprotein nitrogen, 31 to 50 mg.%; carbon dioxide content, 18.7 to 23.4 mEq./L., chloride, 95 to 106 mEq./L.; sodium, 133 to 148 mEq./L.; potassium, 2.8, 3.3, 3.7, 4.4 and 3.4 mEq./L. The serum alkaline phosphatase activity was 3.7 Bodansky units. Urinary diastase on the second hospital day was 170 units. Microscopic study of two stool specimens stained with Sudan IV revealed no fat globules. Urine tested with Sulkowitch's reagent showed a faint turbidity on the fourth hospital day, when the serum calcium concentration was 7.6 mg.%; the serum phosphorus concentration at this time was 3.6 mg.%, and the electrocardiographic tracings showed only slight prolongation of the QT interval

(figure 1). The urine Sulkowitch's test remained normal for the balance of the patient's life.

Postmortem examination was performed six hours after death by Dr. S. N. Cohen. The autopsy was restricted to examination of the body, since permission to examine the head was not granted. The anatomic diagnoses were: acute bronchopneumonia, right lower lobe; aspiration of gastric contents into the tracheobronchial tree, with bilateral acute bronchitis; bilateral apical pulmonary fibrosis with focal calcification and heterotopic bone formation, and with calcification of hilar nodes; bilateral fibrous pleural adhesions; passive congestion of the liver; generalized atherosclerosis, including coronary artery involvement; senile nephrosclerosis with healed infarct of the right kidney; focal healed pyelonephritis; fatty ingrowth of the pancreas; cholesterolosis of the gall-bladder; incarcerated left indirect inguinal hernia.

Careful examination of the neck region revealed several yellow tissue nodules, 1 to 2 mm. in diameter, that grossly might have been parathyroid glands; only one of these proved histologically to be parathyroid. This gland was not weighed. Both principal and oxyphil cells were present, and the gland was quite cellular. The tissue appeared to be normal (figure 2). The adrenals were normal.

Discussion

Criteria for the diagnosis of idiopathic hypoparathyroidism are well defined and include: low concentration of serum calcium, high serum inorganic phosphorus concentration, chronic tetany, absence of history or evidence of surgical or other trauma in the parathyroid region; absence of other causes of hypocalcemia, such as renal insufficiency, malabsorption syndromes, renal tubular acidosis, or nutritional deficiency of vitamin D.

The case described satisfied all of these criteria, but review of the clinical findings revealed only meager evidence of features often associated with hypoparathyroidism. Tetany, latent or manifest, is probably the most characteristic clinical feature of this disease. Tetany occurred in 78% of the cases reviewed by Steinberg and Waldron,[1] and Chvostek's and Trousseau's signs were said to have been present in every case where they were sought. However, it has been observed that Chvostek's and Trousseau's signs are not invariably reliable indicators of latent hypocalcemic tetany.[36] In 32 cases of idiopathic hypoparathyroidism reported since the review by Steinberg and Waldron, Chvostek's sign was absent in three[5, 21, 28] and Trousseau's sign in four cases.[5, 13, 21, 28] In the case described above, Chvostek's sign could be elicited prior to the parenteral administration of calcium gluconate on the first hospital day but was absent thereafter. There was considerable plantar flexion of the toes and the feet, the latter being associated with shortening of the Achilles tendon. The patient had been confined to bed for only three weeks before admission, and it is possible that protracted pedal spasm may have contributed to the tendon shortening. The plantar flexion of the toes disappeared concomitantly with the restoration of the serum calcium concentration toward the normal value.

Convulsions occur in approximately 50% of the cases of idiopathic hypoparathyroidism, but are more common in young people. The enhanced susceptibility of the young to the neuromuscular phenomena of parathyroid deficiency observed in clinical material is in agreement with experimental results showing that neuromuscular irritability after total parathyroidectomy is more profound in young animals (the dog[37] and the sheep[38]).

In the case described above, convulsions occurred 14 years prior to the demonstration of hypocalcemia. Whether the rigidity and convulsions at that time were manifestations of hypocalcemic tetany cannot be determined. The occurrence of postictal hemiparesis and the cerebrospinal fluid characteristics suggest that cerebral vascular disease may have been an important factor. The patient's state of unconsciousness and the unreliability of the history from other sources make assessment of paresthesias, numbness and other subjective features uncertain. It does not seem possible to determine the date of onset of the disease from the neuromuscular manifestations in this case.

More than two thirds of the reported cases of idiopathic hypoparathyroidism have begun before the age of 16. The oldest patients we have found reported in the literature are a 61 year old woman [18] and a 67 year old man.[34] The case here presented of a 79 year old man is therefore the oldest on record.

Cataracts have been observed in approximately half of the cases of idiopathic hypoparathyroidism, and their discovery in young individuals has occasionally led to the correct diagnosis. Cataracts are common in older people, and although the granular cataract typical of hypocalcemic states may be distinguished from senile cataracts, this distinction may be obscured by the coexistence of both types. The cataracts present in our case were thought to be consistent with the type of cataract seen in hypocalcemic states, and showed the lenticular, crystal-shaped, needle-like formations termed "riders." [39]

Since the manifestations of neuromuscular irritability may be minimal in older persons, and ectodermal changes and cataracts are not unusual in this age group, the presence of hypoparathyroid hypocalcemia in the aged may often be unsuspected on clinical grounds. This may actually be a factor in the apparent predominance of young patients among reported cases of idiopathic hypoparathyroidism, and it is possible that the disease may be more common in older persons than is generally believed. In our case, as in several others, hypocalcemia was first suspected as a result of the characteristic electrocardiographic findings of prolongation of the QT interval, associated with lengthening of the ST segment but with normal T wave configuration.[40]

The cause of the hypokalemia in this case was not apparent. Correction of the low serum concentration of potassium was not vigorously pursued, because it was thought that the hypokalemia might tend to alleviate the effects of the low serum calcium concentration, since it has been claimed that tetany may be induced by the administration of potassium salts to subjects who are simultaneously hypokalemic and hypocalcemic,[41] and physiologic studies of neural excitability have shown the similarity between the effects of a decrease in calcium concentration and an increase in potassium concentration.[42]

The existence of hypocalcemia and hyperphosphatemia being established, the diagnosis of idiopathic hypoparathyroidism depends largely upon excluding the presence of other causes of the hypocalcemic state. In the case described, the normal urine specific gravity and the borderline normal serum nonprotein nitrogen concentration suggested that there was no serious impairment of renal function such as might lead to phosphate retention and hypocalcemia. The acid pH of the urine and the absence of calciuria were inconsistent with renal tubular acidosis. The normal bone density in roentgenograms of the skull and chest, as well as the normal serum alkaline phosphatase, suggested that osteomalacia was un-

likely. There was, further, no reason to suspect a malabsorption syndrome in the absence of a history of diarrhea, abdominal surgery or jaundice; clinical signs of vitamin or calorie deficiency were lacking, and stool specimens contained little fat. Acute pancreatitis was clinically unlikely: the urine diastase was normal, and postmortem study revealed no evidence of this condition.

No study was made of the phosphaturic response to administered parathyroid extract (Ellsworth-Howard test), a procedure recommended to distinguish pseudohypoparathyroidism from true hypoparathyroidism. However, the absence of such clinical features as subcutaneous calcification, short stature, round

TABLE 1

Autopsy Findings in Idiopathic Hypoparathyroidism

Reference	Sex	Age (years)		Parathyroids	Other Endocrine Glands
		At Onset	At Death		
35	M	15	16	None found	Adrenal cortical atrophy; lymphocytic infiltration of pituitary and basophil degranulation
48	M	4	13	Fatty replacement of glands. Single scattered parenchymal cells noted	Increase in pituitary basophils
49	F	3½	12	Absent	No abnormality
50	F	3	11	Absent	Adrenal atrophy with cortical destruction; small pituitary
51	M	13	?	Absent	"Practically no trace of adrenals"
19	F	3	4	No gross tissue found; possibly bits of atrophic tissue	Bilateral adrenal atrophy
28	F	10	30	Absent	Bilateral adrenocortical atrophy
Present case	M	?65	79	One gland found, histologically normal	No abnormality

face, shortened metacarpals and mental deficiency, almost always present in pseudohypoparathyroidism,[43] together with the age of the patient, seemed to make pseudohypoparathyroidism a most unlikely diagnostic possibility.

There have been only seven reported instances of postmortem examination in cases of idiopathic hypoparathyroidism. The findings in these cases and in the present case are summarized in table 1. The demonstration of the presence of apparently normal parathyroid tissue in a case satisfying the clinical criteria of hypoparathyroidism is unique. No evidence of parathyroid tissue was found in five of the seven previously reported autopsies, and only traces of such tissue were found in the other two cases. Erdheim could not find parathyroid glands

in cases of postoperative tetany, even when many serial sections of the entire neck were made,[44] and it has been claimed that even one remaining parathyroid gland will prevent the occurrence of hypoparathyroidism after thyroid surgery.[45] The present case fulfilled all of the clinical criteria for the diagnosis of idiopathic hypoparathyroidism, but careful postmortem examination revealed the presence of one histologically normal parathyroid gland.

It is generally accepted that a decrease in the concentration of serum calcium is a stimulus to parathyroid secretion. If the hypocalcemia in the present case was chronic, as the history suggests it may have been, then secondary hyperplasia of parathyroid tissue might have been expected, as has been observed in other hypocalcemic states (such as renal disease and malabsorption syndromes, and also pseudohypoparathyroidism[46]). The absence of enlargement of the parathyroid glands could therefore be interpreted as further evidence in support of the diagnosis of hypoparathyroidism. The presence of the single normal-looking parathyroid need not necessarily mean that the secretion of parathyroid hormone had been adequate. A possibly analogous situation exists in the occurrence of small areas of follicular thyroid tissue in the atrophied thyroid gland of some cases of primary myxedema.[47] If the hypoparathyroidism in this case was of relatively recent origin, it is conceivable that physiologic function of the gland had ceased before anatomic changes were evident, and that the latter might have required a longer time for their development. In view of the presence of normal-appearing parathyroid tissue, in this case, which satisfied the clinical and laboratory criteria of idiopathic hypoparathyroidism, the possibility remains that parathyroid function may have been normal, and that the hypocalcemia and hyperphosphatemia may have been the result of unknown factors. If this was the case, then this represents an example of "pseudohypoparathyroidism" of a kind distinctly different from that usually so designated,[43, 46] and it raises the further possibility, in view of the absence of published postmortem studies in adult "idiopathic hypoparathyroidism," that this clinical syndrome may not necessarily be a consequence of parathyroid insufficiency.

Drake and associates[48] noted that the age distribution in 11 cases of hypoparathyroidism suggested two distinct populations, and they raised the possibility that idiopathic hypoparathyroidism might result from more than one cause. Review of over 100 cases did not reveal as distinct a separation of cases on the basis of age at onset, but there did appear to be some tendency for a higher incidence in childhood and again in the fourth decade (figure 3). It is also noteworthy that in all of the previously reported autopsied cases the onset of the disease occurred before the age of 16 years; three of these patients developed clinical Addison's disease several years after the onset of hypoparathyroidism,[28, 50, 51] and another patient had adrenal atrophy.[19] One patient developed hypoparathyroidism within a few months after clinical Addison's disease appeared.[35] Another death occurred within one year after the onset of idiopathic hypoparathyroidism,[48] and in the seventh case the endocrine glands, with the exception of the absent parathyroids, were normal.[49]

Summary

A 79 year old man presented clinical and laboratory findings satisfying the criteria for the diagnosis of idiopathic hypoparathyroidism. At autopsy a single

parathyroid gland was found which histologically appeared normal. The possible implications of these findings are discussed.

Summario in Interlingua

Hypoparathyroidismo es pauco commun. Illo occurre predominantemente in juvene subjectos. Reportos de casos necropsiate es infrequente. Le casos in le litteratura que se terminava in le morte del patiente esseva frequentemente associate con morbo de Addison. Le constatation post morte de normal tissu parathyroidic non es mentionate in ulle previe reporto.

Un masculo de racia blanc de 79 annos de etate esseva admittite al hospital a causa de tusse, febre, e stupor progressive. Depost quatro menses ille habeva suffrite recurrente attaccos convulsive que non esseva subjugabile con phenobarbital. Le examine physic revelava febre, dyspnea, cataractas bilateral, e signos de pneumonia.

Un electrocardiogramma prendite brevemente post le admission al hospital suggereva hypocalciemia. A iste tempore un positive signo de Chvostek esseva evocate. Le calcium del sero amontava a 5,0 mg in 100 ml, le phosphoro a 7,6 mg in 100 ml.

Le function renal esseva considerate como adequate super le base del valores trovate pro le nitrogeno non ligate a proteina e pro le gravitate specific del urina. Le observation de un densitate normal del osso in radiographias del cranio, del manos, e del thorace, insimul con le valor normal de phosphatase alcalin, serviva a justificar le exclusion de un diagnose de osteomalacia. Esseva incontrate nulle indication de malabsorption intestinal o de carentia de vitamina. Le anamnese revelava nulle occurrentia de pancreatitis e nulle exposition a agentes chimic que tende a ligar calcium. Le etate del patiente e le absentia del aspectos characteristic de pseudohypoparathyroidismo rendeva improbabile le diagnose de iste ultime condition. Le documentation anamnestic e le examine physic non indicava ulle occurrentia passate de trauma chirurgic o accidental in le collo.

Le patiente respondeva al therapia antibiotic e al tractamento con gluconato de calcium per via intravenose e con lactato de calcium e vitamina D per via oral. Le temperatura redeveniva normal. Le electrocardiogramma se meliorava. Le signo de Chvostek deveniva negative. Le test urinari de Sulkowitch deveniva positive. E le stato clinic del patiente esseva melior. Le septime die del sojorno al hospital, le febre recurreva. Le condition del patiente se deteriorava. Ille moriva le sequente die.

Le examine post morte revelava le presentia de un sol glandula parathyroidic que esseva histologicamente normal. Iste constatation singular, in un caso characterisate per le aspectos clinic de hypoparathyroidismo idiopathic, non esseva facile a explicar. Possibilemente le production de hormon parathyroidic esseva inadequate o non-responsivitate a iste substantia se habeva disveloppate. Del altere latere, il es etiam possibile que conditiones pathologic que satisface le criterios usual pro le diagnose de hypoparathyroidismo idiopathic es non semper causate per carentia de hormon parathyroidic.

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VITAMIN D POISONING: A REPORT OF TWO CASES*

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IN 1942, two of the earliest cases in the literature of vitamin D poisoning in adults were described by Tumulty and Howard.[1] Since that time many reports have appeared and the clinical picture has been well described, particularly by Howard and Meyer in 1948[2] and by Chaplin et al. in 1951.[3]

Despite its toxicity, vitamin D continues to be used with little or no justification in conditions such as sarcoidosis, asthma, psoriasis, and rheumatoid arthritis, and often results in poisoning. In addition, the availability of highly concentrated preparations of vitamin D has led to intoxication resulting from self-medication.[4]

In the two patients here described, vitamin D was used for specific deficiency states, namely, osteomalacia secondary to steatorrhea, and hypoparathyroidism after thyroidectomy. In both conditions, larger doses of vitamin D than are required in juvenile rickets are necessary to produce a therapeutic effect. Nevertheless, poisoning occurred; in the first patient it followed treatment with a gluten-free diet; in the second there was no obvious precipitating cause.

CASE REPORTS

Case 1. A spinster, aged 59, was admitted to hospital on April 30, 1958, with a two-month history of increasing thirst, constipation, frequency of micturition, and lassitude. In January, 1957, she had been investigated for idiopathic steatorrhea complicated by iron deficiency anemia and osteomalacia. At that time her hemoglobin was 5.9 gm. per 100 ml., with an MCHC of 22%. The serum calcium was 7.8 mg. per 100 ml.; alkaline phosphatase, 41 units per 100 ml. The patient was treated with oral and parenteral iron, folic acid, vitamin D, 25,000 units, and calcium lactate, 15 gm. daily. In April, 1957, she was re-admitted because of further loss of weight and diarrhea. Her hemoglobin was then 14.8 gm. per 100 ml.; serum calcium, 9.0 mg. per 100 ml. The diarrhea responded within one month to a gluten-free diet.

On admission in April, 1958, the patient was ill, depressed and anemic. The blood pressure had risen to 170/100 mm. Hg (previously, 120/80 mm. Hg).

Laboratory Investigations: Hemoglobin was 9.8 gm. per 100 ml., and the film showed hypochromic microcytic red cells. The urine contained a trace of protein, with a fixed specific gravity of 1.005. No casts were seen. The urinary output was 2.1 L. in 24 hours. The serum calcium was 13.8 mg. per 100 ml.; plasma phosphorus, 3.5 mg. per 100 ml.; alkaline phosphatase, 8 units per 100 ml. The blood urea was 72 mg. per 100 ml. An electrocardiogram showed normal curves.

Treatment and Progress: It seemed likely that, with a gluten-free diet, absorption of calcium had improved, with consequent hypercalcemia and renal failure. Vitamin D and calcium lactate were therefore discontinued, a diet low in calcium (approximately 350 mg. daily) and protein (approximately 30 gm. daily) was given, and the patient was allowed to drink large quantities of water. She rapidly improved, and the blood pressure fell to 110/70 mm. Hg. Within two weeks the serum calcium

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fell to 9.5 mg. per 100 ml., plasma phosphorus to 2.8 mg. per 100 ml., and blood urea to 31 mg. per 100 ml. Despite 1,500 mg. of parenteral iron, she remained anemic (9.2 gm. hemoglobin per 100 ml.). Examination of the bone marrow showed micronormoblastic erythropoiesis with ample stores of iron.

The patient has remained well, and four months after discharge her hemoglobin was 13 gm. per 100 ml., and the red cells were morphologically normal.

Case 2. A housewife, aged 53, was admitted to hospital on June 17, 1958, with a two-month history of lassitude, loss of weight, thirst, frequency of micturition, vomiting and constipation. In 1936 she had had a partial thyroidectomy for thyrotoxicosis. From 1939 until 1956 she had been treated with thyroid, calcium and vitamin D intermittently for myxedema and tetany. Since then (1956), she had been taking by mouth thyroid, 2 gr., calcum lactate, 2 gm., and vitamin D, 500,000 units daily.

On admission the patient was ill and anemic. There was no evidence of tetany. The blood pressure was 180/100 mm. Hg.

Laboratory Investigations: Examination of the blood showed hemoglobin, 7.4 gm. per 100 ml., with hypochromic microcytic red cells. The urine contained a small amount of protein, with a fixed specific gravity of 1.005. There were no casts. The urinary output was 3.2 L. in 24 hours. The serum calcium was 13.4 mg. per 100 ml.; plasma phosphorus, 4.2 mg. per 100 ml.; alkaline phosphatase, 17 units per 100 ml. The blood urea was 156 mg. per 100 ml. An electrocardiogram showed normal curves.

Treatment and Progress: Although this patient had required large doses of vitamin D and calcium lactate to control her tetany over the previous two years, hypercalcemia had eventually resulted. These drugs were therefore discontinued, and she was encouraged to drink large quantities of water. A diet low in calcium (approximately 500 mg. daily) and protein (approximately 40 gm. daily) was also given. She rapidly improved, and her blood pressure fell to 130/80 mm. Hg. Within four weeks the serum calcium fell to 10.9 mg. per 100 ml., plasma phosphorus to 3.3 mg. per 100 ml., and blood urea to 69 mg. per 100 ml. The patient remained mildly anemic, with a hemoglobin of 10.4 gm. per 100 ml., despite 1,300 mg. of parenteral iron.

Three months later the patent was well, with a blood pressure of 140/90 mm. Hg. Her hemoglobin was 11.0 gm. per 100 ml., and the red cells were morphologically normal. The serum calcium was 9.7 mg. per 100 ml.; plasma phosphorus, 3.6 mg. per 100 ml.; alkaline phosphatase, 13 units per 100 ml.; blood urea, 79 mg. per 100 ml. The patient had not developed tetany since the vitamin D and calcium lactate were stopped on June 17, 1958.

Discussion

Albright and Reifenstein[5] believe that poisoning is due primarily to vitamin D promoting absorption of calcium from the gut, with consequent hypercalcemia. This results in depression of the parathyroid glands, with a fall in urinary phosphorus excretion, and so hyperphosphatemia. The blood therefore becomes supersaturated with calcium and phosphate ions, and calcium phosphate is precipitated, causing tissue necrosis. A secondary effect of vitamin D, which these authors believe to be less important in the production of poisoning, is an increase in urinary phosphorus excretion. This, in turn, leads to hypophosphatemia, and so to hypercalcemia. Thus hypercalcemia, while usually accompanied by hyperphosphatemia, may also be associated with hypophosphatemia.

In contrast, Reed and his colleagues[6] regard the toxicity of vitamin D as being due to a local effect on the kidneys, causing tissue necrosis with secondary renal calcification without, necessarily, the appearance of hypercalcemia.

Whatever the mechanism, the dose required to produce poisoning is very variable. It has been recorded after 12 days at 750,000 units daily,[1] while other examples have been noted after as little as 50,000 units daily for a few weeks. On the other hand, some patients may tolerate as much as 500,000 units daily for from six to 12 months. Indeed, it has been suggested that very large doses of vitamin D and calcium are required in osteomalacia secondary to steatorrhea,[7] since malabsorption of the former may lead to poor absorption of the latter. In addition, calcium may combine with fatty acids to form soaps in the intestine, and so not be absorbed. Finally, calcium is also directly involved in the malabsorption defect. Thus their patients were cured, but only slowly, on vitamin D, 10,000 units parenterally, or 50,000 units and 15 to 30 gm. calcium lactate by mouth daily. Doses as high as 100,000 to 150,000 units daily were used by Anderson[8] and Strang.[9] Unfortunately, in the first patient described, the effect of a gluten-free diet in increasing the absorption of calcium was not appreciated, and poisoning resulted.

In hypoparathyroidism, most patients need 100,000 to 300,000 units daily, with added calcium.[2] Thus McLean[10] thought that the risk of poisoning with vitamin D in this condition may be disregarded, although in fact Howard and Meyer's[2] patient became poisoned after 300,000 units daily for two weeks. Nevertheless, our second patient, who had been given large doses of vitamin D and calcium lactate intermittently for 19 years without disaster, suddenly developed hypercalcemia without obvious cause.

The clinical picture of vitamin D poisoning is due to hypercalcemia per se, and to renal failure. The former causes fatigue, depression, loss of weight,[2] and shortening of the ST segment and QT interval of the electrocardiogram.[11] In both of our patients the electrocardiogram was normal. The renal failure causes polyuria, with a low fixed specific gravity urine and a moderate rise in the blood urea. Proteinuria is minimal, and formed elements are often absent. Both of our patients had moderate reversible hypertension; thirst and constipation were conspicuous. This was in contrast to the experience of Scharfman and Propp,[12] who found that the blood pressure was unaffected, and to that of Chaplin et al.,[3] who recorded diarrhea in their patients. A normocytic, normochromic anemia invariably occurs and is associated with the uremia.[12] While both of our patients initially had lack of iron, parenteral iron failed to correct the anemia until the kidneys had recovered normal function. Loge et al.[13] have shown that the principal factor responsible for the anemia is invariably depression of erythropoiesis, with defective utilization of iron. Occasionally, hemolysis and loss of blood are partly responsible. It seems likely, therefore, that the fatigue, weakness and depression may well be due to the anemia rather than to the hypercalcemia.

Vitamin D poisoning may result in metastatic calcification affecting the kidneys, blood vessels, lungs, and other soft tissues.[14] However, neither patient was examined for ocular deposits of calcium and band keratitis, as described by Howard and Meyer,[2] while demineralization of the bones and metastatic calcification,[3] although searched for, were not found.

The diagnosis is dependent upon the history of vitamin D intake, the triad of anemia, azotemia and hypercalcemia, and, finally, an awareness of the possibility of overdosage.

In the differential diagnosis of hypercalcemia, myelomatosis may be excluded by examination of the serum proteins, bone marrow, and radiographs. In primary hyperparathyroidism, there is a considerably elevated alkaline phosphatase, with hypophosphatemia in the absence of renal failure. Sarcoidosis may be diagnosed by the pulmonary infiltration and hilar adenopathy detected radiographically. Finally, in hypercalcemia of the milk-alkali syndrome,[15] the history is all-important.

The prognosis is very variable, and is dependent upon individual susceptibility and the degree of renal failure. Indeed, the latter and consequent hypertension may be permanent and even fatal.[3]

The most important therapeutic measure is to stop the vitamin D and calcium lactate. Since excessive absorption of calcium is impossible in the absence or lack of calcium in the diet, a diet low in calcium is obviously necessary. In the presence of renal failure, adequate fluids and a diet low in protein should be given. Cortisone has been recorded as being antagonistic to vitamin D in the hypercalcemia of sarcoidosis,[16] but in neither patient described was it required. Fortunately, recovery was complete in both patients. Prevention of poisoning with vitamin D depends upon continuous surveillance of all patients receiving this drug, which, of course, should be used only in specific deficiency states. There is no risk of overdosage provided there is no hypercalcemia.

Summary

Two patients with vitamin D poisoning are described. In both, the drug was being used for specific deficiency states.

Hypercalcemia resulted: in the first, after the introduction of a gluten-free diet for idiopathic steatorrhea; in the second, with hypoparathyroidism, from no apparent cause.

The clinical picture and treatment of the resultant renal failure are described and reviewed.

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Summario in Interlingua

Le historia de intoxication per vitamina D es revistate. Duo patientes con iste condition es describite. In ambes, le droga esseva usate pro specific statos de deficientia: In le prime pro steatorrhea idiopathic e in le secunde pro hypoparathyroidismo post thyroidectomia. Hypercalciemia esseva presente in ambe patientes. In le prime del duo casos, il esseva opinate que le causa precipitatori esseva le introduction de un dieta sin glutine, sed in le secunde caso nulle factor precipitatori esseva apparente.

Le intoxication in tal casos resulta del facto que le vitamina D promove le absorption intestinal de calcium con le effecto consequente de hypercalciemia. Un effecto secundari del vitamina D es le augmento del excretion urinari de phosphoro. Isto resulta in hypophosphatemia e assi de novo in hypercalciemia.

Le quantitate de vitamina D requirite pro producer intoxication es multo variabile, sed in le statos de deficientia representate per le hic describite casos, grande doses—il es ver—es therapeuticamente necessari. Le tableau clinic del intoxication es illo de hypercalciemia con disfallimento renal resultante in anemia. In le diagnose differential, le possibilitate de myelomatosis, hyperparathyroidismo primari, e syndrome alcalin per lacte debe esser excludite.

Le prognose depende del susceptibilitate individual e del grado de disfallimento renal. Il occurre que iste secunde—le disfallimento renal—es permanente e mesmo que illo es letal. Le tractamento consiste in discontinuar le administration del droga, in prescriber un dieta a basse contento de calcium, e in tractar le disfallimento renal. Le prevention de intoxication per vitamina D require le continue observation de omne patientes qui se trova sub tractamento con iste droga.

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BENIGN PAROXYSMAL VENTRICULAR TACHYCARDIA: REPORT OF A CASE*

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That paroxysmal ventricular tachycardia may occur in the absence of underlying organic heart disease has been established by numerous individual case reports [1-14] and studies of large groups of cases of paroxysmal ventricular tachycardia.[15-20] It is, however, a relatively uncommon disorder. In contrast to the

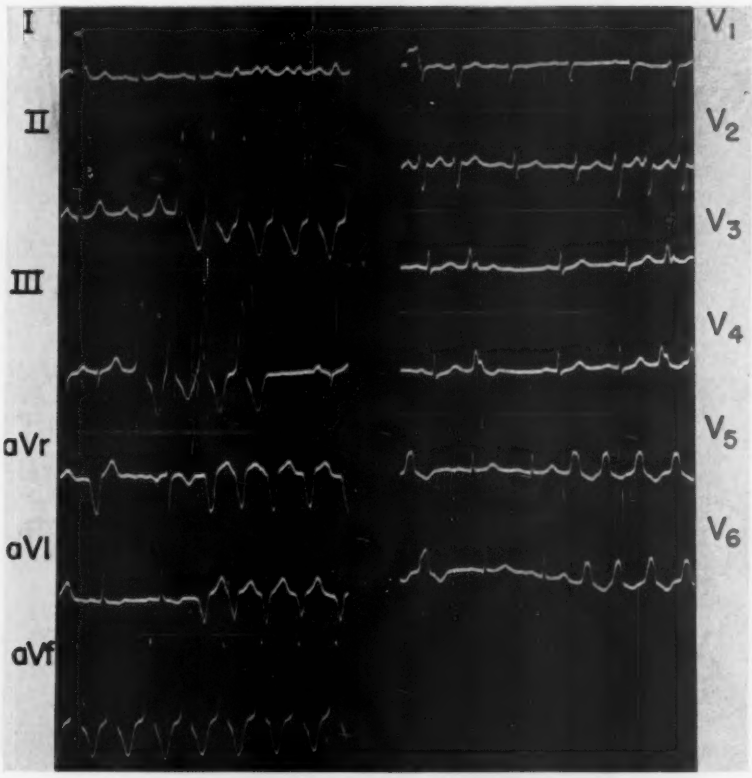

Fig. 1. Electrocardiogram dated January 24, 1955. Short runs of paroxysmal ventricular tachycardia are present. In V_3 and V_4 isolated ventricular prematurities are noted. The normally conducted P-QRS-T complexes seen throughout the tracing are not unusual.

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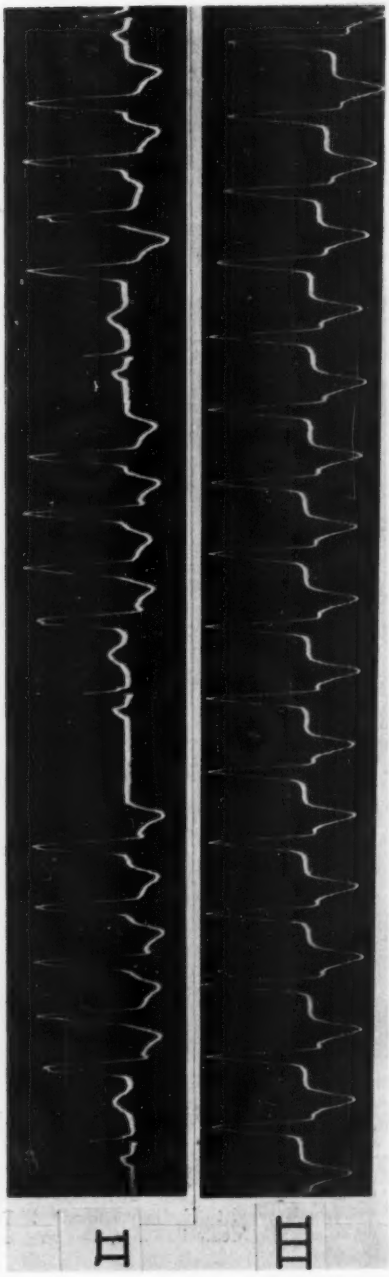

FIG. 2. Electrocardiographic tracings dated May 11, 1959. Lead II shows short runs of four and five ventricular complexes. Lead III shows a more prolonged episode of paroxysmal ventricular tachycardia.

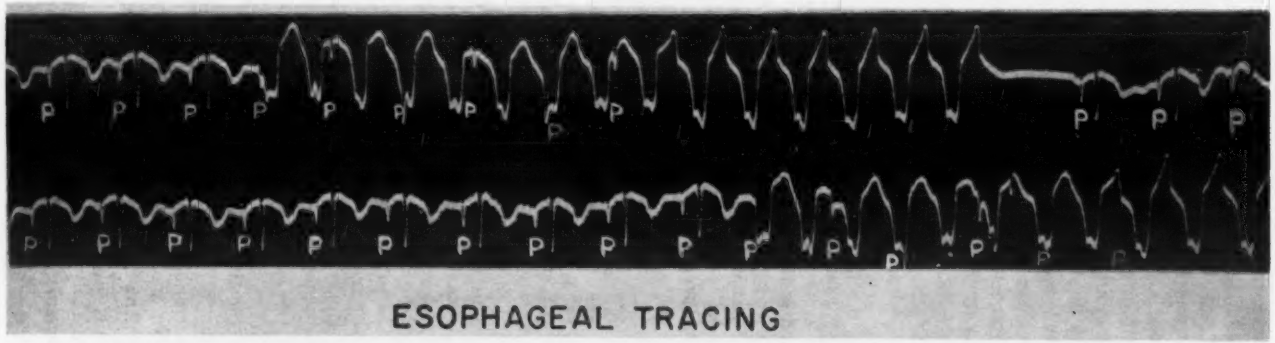

FIG. 3. Two strips of a continuous esophageal lead. Each strip contains a short burst of paroxysmal ventricular tachycardia. During the early portion of each paroxysm, P waves continue to occur, deforming the contour of the ventricular complexes but bearing no constant relationship to them. During the latter portion of the paroxysm the P waves disappear, indicating sinus arrest, and the contour of the ventricular complexes becomes uniform. When the paroxysm ceases in the first strip, there is a prolonged pause before the normal sinus rhythm is resumed, again indicating that the sinus node has been quiescent during the latter portion of the paroxysm.

ominous prognosis of paroxysmal ventricular tachycardia associated with organic heart disease,[15, 20] this arrythmia, occurring without underlying heart disease, is generally a benign disorder and the prognosis is good.[12, 20] The patients are usually well except during paroxysms, when they may have symptoms of palpitation,[2, 5, 9, 10] dizziness,[5] syncope,[5, 12] and sensations of pressure in the chest.[2, 7] Some patients have been entirely asymptomatic even during paroxysms, and completely unaware of their condition.[3] That the condition is not always entirely benign is demonstrated by the fact that sudden death,[8, 20] pulmonary edema,[9] congestive heart failure,[13] and death from a prolonged attack [6] have been reported during paroxysms in these patients.

The following case is of interest because of the long period of time (four years) over which the patient's arrythmia has been documented by electrocardiographic tracings, the multiplicity of her paroxysms, her almost completely asymptomatic state, and the proof of the nature of her arrythmia furnished by the esophageal lead.

Case Report

In January, 1955, this white woman, then 61 years old, presented at the outpatient department with palpitations of from six to seven years' duration. These episodes occurred about once a week, and lasted from one minute to 24 hours. They were more frequent following exertion or emotional stress. They were not associated with chest pain, dizziness, syncope, shortness of breath or pedal edema. There was no previous history of heart disease. Physical examination revealed a blood pressure of 125/80 mm. of Hg. There was no congestion of the neck veins. The lungs were clear. The heart revealed short runs of tachycardia. There was no cardiac enlargement, and no thrills or murmurs. The abdomen and extremities were normal. The electrocardiogram revealed short runs of paroxysmal ventricular tachycardia (figure 1) but was otherwise within normal limits. Master's two-step examination was negative. The chest x-ray was within normal limits. The I^{131} uptake by the thyroid gland was 17%. The blood count, urinalysis, serology, blood urea, sedimentation rate, and glucose tolerance test were normal. The serum cholesterol was 381 mg.%

The patient has been followed in the outpatient clinic for four years. She continues to be active and asymptomatic except for the sensation of palpitations, which now occurs about three to four times daily and lasts about one minute. The electrocardiogram continues to be normal when a sinus rhythm is present. Short bursts and an occasional long run of 40 to 50 complexes of paroxysmal ventricular tachycardia are present (figure 2). The patient seems to be unaware of the shorter bursts. Figure 3 is an electrocardiogram recorded with the esophageal lead in 1956. It demonstrates the occurrence of P waves completely dissociated from the QRS complexes during paroxysms of ventricular tachycardia. Quinidine, 0.4 gm. every four hours, and Pronestyl, 250 mg. every four hours, have been without effect on her arrhythmia.

Discussion

In 1932 Frank N. Wilson et al.[1] wrote a lucid description of this condition, in which they made use of descriptions, terminology, and classification previously presented by Louis Gallavardin and associates in France. This paper, as well as a more recent one by Froment et al. divides into two types the paroxysmal ventricular tachycardia occurring in the absence of apparent organic heart disease. In one type the paroxysms are likely to be more prolonged and rather infrequent. In the interim between paroxysms, extrasystoles are not present with unusual frequency. Froment et al.[12] postulate an irritable focus in the septum, and prob-

ably a histologic lesion of the conducting mechanism, to account for this type of arrythmia. In the other type the paroxysms are much more frequent and usually of brief duration, although more prolonged attacks, lasting for hours or days, occasionally occur. In the interval between paroxysms, ventricular premature systoles, occurring either singly or in short bursts, are an almost constant finding. The paroxysms are more likely to occur following exertion or emotional stress. Froment et al.[12] postulate a microscopic myocardial lesion, probably of the bundle of His, acting as an irritable focus to produce this type of arrythmia.

The case presented in this paper is of the latter type. Because of the patient's age, arteriosclerotic heart disease cannot be entirely ruled out, although there are no clinical manifestations of heart disease apart from her arrythmia. Procaine amide hydrochloride and quinidine were of no benefit to this patient, but have been reported by others [2, 3, 5, 11, 13] to be effective in cases of this type.

Summary

A case is described of benign paroxysmal ventricular tachycardia occurring in the absence of demonstrable organic heart disease.

Summario in Interlingua

Paroxysmic tachycardia ventricular, occurrente como condition benigne in le absentia de un subjacente organic morbo cardiac se trova frequentemente reportate in le litteratura. Le prognose es usualmente bon, e le patientes es usualmente libere de symptomas con le exception del symptomas producite per le arrhythmia mesme.

Le presente reporto describe le caso de un femina de 65 annos de etate qui habeva iste condition. Le caso es de interesse a causa del longe periodo de tempore—quatro annos—pro le qual le presentia del arrhythmia es documentate in registrationes electrocardiographic. Iste registrationes monstra un multiplicitate de attaccos. Le stato del patiente esseva asymptomatic. Therapia a quinidina e Pronestyl esseva sin effecto.

Benigne tachycardia ventricular paroxysmic occurre in duo typos clinic. In le un, le paroxysmos es plus tosto infrequente. Illos tende a esser prolongate. Durante le intervallos inter le attaccos, prematur systoles ventricular non occurre con un frequentia plus que usual. In le secunde typo, le paroxysmos es multo plus frequente. Lor duration es usualmente breve. E durante le intervallos inter le attaccos, prematur systoles ventricular es un constatation quasi constante. Le presente caso es del secunde typo. Il es probabile que lesiones microscopic in le mechanismo de conduction age como focos de irritation e es responsabile pro le arrhythmias.

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NORMOCHOLESTEROLEMIC XANTHOMATOSIS: REPORT OF A CASE WITH MYOCARDIAL FIBROSIS AND MYELOSCLEROSIS*

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The xanthomatoses are usually classified in two groups, one with normal, the other with raised levels of cholesterol in the blood. The first comprises Hand-Schüller-Christian disease, Letterer-Siwe disease, eosinophilic granuloma,

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and a number of *formes frustes* and mixtures of these. That these conditions, so diverse in their clinical presentation, are histologically similar is generally agreed.[4] Rowland[8] in 1928 showed that the foam cells which dermatologists had long known to be characteristic of the skin lesions of xanthoma disseminatum were also to be found in various tissues in Hand-Schüller-Christian disease, although the two conditions are rarely found in the same patient, and then almost always in adults.[1]

The present paper reports a middle aged woman who first presented at a dermatologic clinic because of xanthoma disseminatum, and who died 17 years later, having developed systemic xanthomatosis with extensive involvement of bone and, uniquely, the myocardium, to such an extent that a grossly abnormal electrocardiographic pattern was produced. The blood cholesterol level remained normal throughout the period of observation.

Case Report

In 1949 this patient, then aged 49, presented the classic picture of xanthoma disseminatum. She had first noticed red spots on each side of the neck in 1940, their size and number steadily increasing and their color becoming browner as time went on, until in 1949 lesions were to be seen across the face, neck, shoulders, upper and outer parts of the arms, in a wide V over the front of the chest, in the groins, and in the mucous membranes of the upper lip, cheeks, soft palate, pharynx, and epiglottis (figure 1).

The lesions varied in appearance according to their age and distribution, but all were soft and rather velvety to the touch, with unbroken surfaces. They did not itch, and did not give rise to pain unless, for example, caught by a comb. Chamois-leather yellow plaques of xanthelasma were present on the eyelids, especially at their inner ends, and flat yellow papules were found on the chin. At the temples and in front of the ears were areas of reddish purple staining, and a few sepia maculopapules were scattered over the rest of the face. Similar discrete papules, ranging in diameter from 1 mm. to 0.5 cm., were to be seen on the chest, but about the neck and shoulders they were confluent. The flattened papules in the oral mucous membrane were of a yellowish pink colour.

The patient had had good health since childhood except that her second pregnancy had been followed by several attacks of phlebitis of the legs. Also, from about 1945 on she had suffered from some pain in the knees. In 1947 she had become a little hoarse, and this hoarseness and weakness of the voice persisted until her death. By 1949 some dyspnea had developed, and direct laryngoscopy revealed the presence of fibrous nodules in the larynx. A biopsy specimen taken from the posterior pharyngeal wall was examined by the late Professor Matthew Stewart, who described it as "a typical fibrosing xanthoma of long standing. There is a tumorlike mass lying between the squamous epithelium and the underlying striped muscle. For the most part there is a very sharp margin to the nodule, but elsewhere striped muscle is incorporated within it and this to a considerable extent. Foamy cells are present in good number. Besides fibrosis there is active cellular proliferation—fibroblasts—with the formation of many giant cells, none of them of Langhans type."

Biopsy of the skin, also in 1949, showed a normal epidermis in the mature lesions, and a dermis infiltrated by fibrous tissue, numerous actively proliferating fibroblasts, collections of foam cells, and some Touton giant cells (figure 2). Frozen sections were seen under the polarizing microscope to contain optically active lipoid, and special staining indicated that cholesterol was present in the foam cells.

The general condition of the patient at that time was very good, but the blood

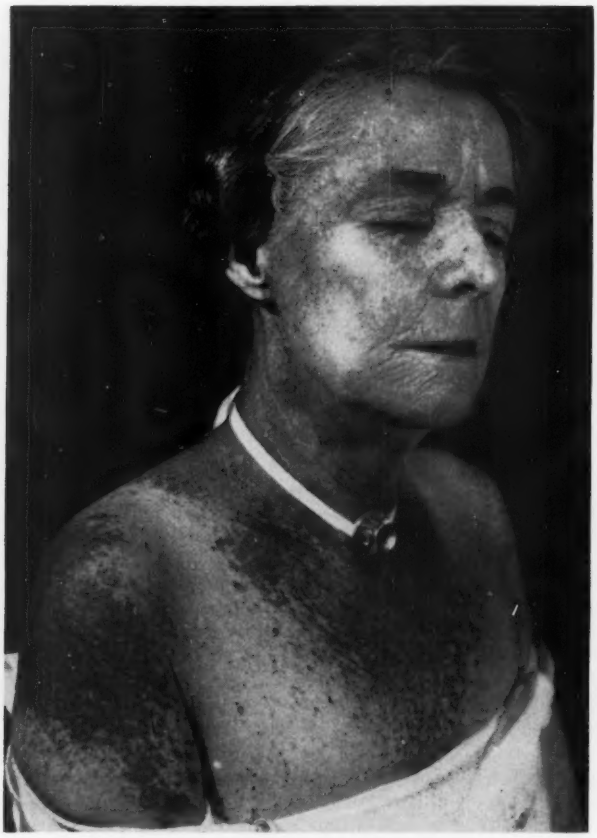

FIG. 1. Appearance in 1953.

pressure was 170/90 mm. of Hg. The electrocardiogram was normal except for sinus tachycardia, and radiography of the chest showed slight unfolding of the aorta but no cardiac enlargement. There was no albuminuria or glycosuria, and the blood cholesterol was 120 mg. per 100 ml.

Dyspnea gradually became more troublesome, until in 1953 a permanent tracheostomy was established. This did not entirely relieve the respiratory embarrassment, some breathlessness on exertion remaining, although no physical signs of cardiac or pulmonary disease were to be found, and the chest film was normal. Several attacks of "bronchitis," in which quantities of mucoid sputum were expectorated, and which caused marked cyanosis, occurred during the winter, and in April, 1954, a few days after an upper respiratory tract infection, the blood pressure rose to 210/100 mm. of Hg, and gross edema appeared in the legs and left arm. There was albuminuria, and the chest film now showed slight cardiac enlargement, but the electrocardiogram was still normal.

Albuminuria persisted for three months, and varied in quantity from day to day during the first two weeks (from 0.5 to 11 gm. per liter [Esbach]). Edema cleared

more rapidly, and the blood pressure returned to its former level of 180/90 mm. of Hg by the middle of May. At no time did the blood urea exceed 43 mg. per 100 ml., but the standard urea clearance at one point fell to 36% of normal. The urine was alkaline in reaction and contained 10 to 30 red cells and the same number of white cells per high power field, with a few epithelial cells.

At the same time severe anemia occurred, being at its worst in early May, when the hemoglobin was 7.4 gm. per 100 ml., red blood cells were 2,600,000 per cubic millimeter, and white blood cells were 5,900 per cubic millimeter. The response to treatment by transfusion and the exhibition of a variety of hematinic agents was poor, the blood picture not returning to normal until five months later.

From October, 1954, until June, 1956, there was little change in the general condition. The patient was able to get about the house but was too breathless to go out. In the skin the early lesions (the dusky red papules) were steadily becoming darker in shade and confluent, while the older, sepia ones became flatter and the epidermis over them thinner.

In June, 1956, there were several attacks of paroxysmal nocturnal dyspnea, and at one point the blood pressure reached 250/110 mm. of Hg. There were marked jugular venous congestion and distention of the veins over the sternum. The liver

FIG. 2. Skin biopsy, 1953. Magnification × 550. A large foam cell is seen in the center of the field.

was palpably enlarged. From that time until her death a year later the patient remained cyanosed, orthopneic, and prone to attacks of cardiac asthma. She also suffered from prolonged bouts of severe breathlessness with cough, during which large amounts of clear mucoid sputum were brought up with some difficulty. On these occasions there was little to make out on physical or radiologic examination of

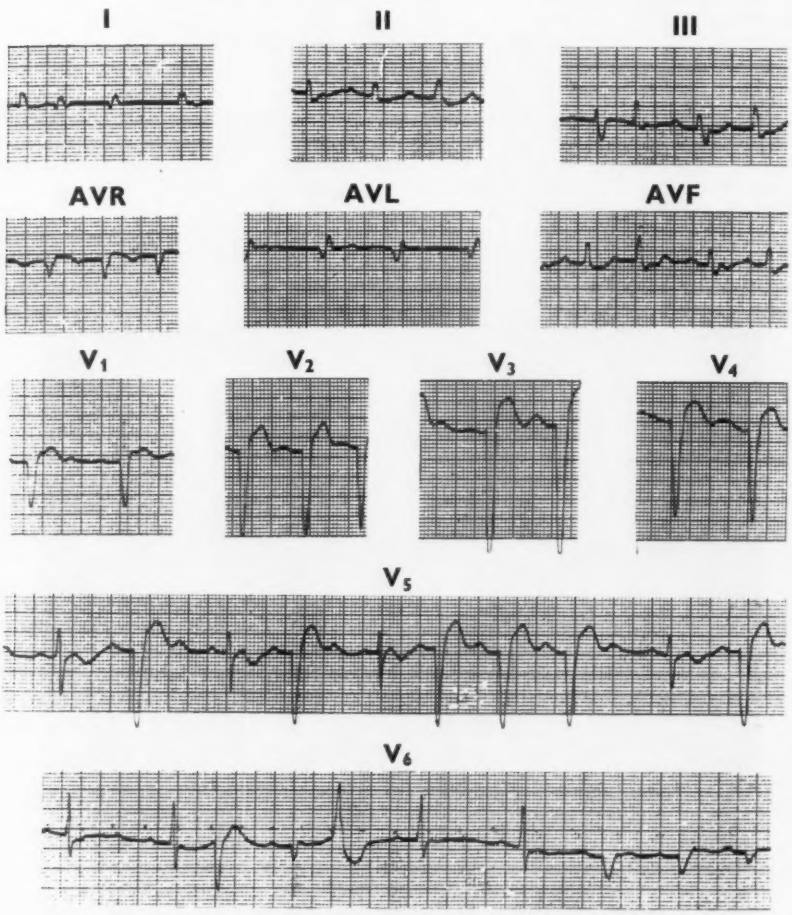

FIG. 3. Electrocardiogram, 1957, showing ventricular ectopic beats and intermittent bundle branch block (V_6).

the chest, and there was no appreciable response to treatment. Unfortunately, the patient was adamant in her refusal to return to hospital, until in June, 1957, the tracheostomy had to be enlarged. Three days later the patient died during an attack of acute dyspnea.

In May, 1957, electrocardiography revealed gross abnormalities for the first time (figure 3): "The basic rhythm appears to be sinus in origin, with frequent ventricular

ectopic beats arising from at least two different foci, and amounting in places to short bursts of ventricular tachycardia. Apart from the ectopic beats, the QRS complex is frequently prolonged beyond 0.12 sec., and there seems to be aberrant interventricular conduction, or intermittent bundle branch block, as for example in V_6. An occasional beat arising in the sinus node is of normal duration, and the T waves are inverted and ischaemic in appearance, e.g., V_5. There is no definite evidence of infarction."

FIG. 4. Radiograph of right knee, showing irregular sclerosis, disordered trabeculation and subperiosteal bone formation.

The last blood examination, performed a week before the patient's death, showed no abnormalities. There was no anemia, and the lipids were low rather than high normal: serum free cholesterol, 40 mg.; ester cholesterol, 80 mg.; phospholipid, 150 mg.; fatty acid, 360 mg.; neutral fat, 200 mg. per 100 ml. The plasma albumin was 3.4 gm.; globulin, 2.0 gm. per 100 ml.

Radiologic Appearances: The bones were x-rayed in 1950, 1951, 1953, 1954 and 1957. Abnormalities were first observed in the tibiae and femora, becoming progressively more widespread and more marked. Eventually the femora, tibiae, humeri, radii and fibulae were involved, the remainder of the skeleton showing no alteration.

In 1950, thickening of the trabeculae at the lower ends of the femora and upper ends of tibiae was seen. The trabecular pattern became steadily more disorganized, and gradually a marked but ill-defined sclerosis, apparently affecting the medulla, developed in the neck, intertrochanteric region and lower ends of the femora, upper and lower thirds of the tibiae and fibulae, upper ends of humeri and lower ends of radii (figure 4). Subperiosteal new bone formation advanced very slowly at the lower end of the femora and both ends of the tibiae. The midshafts of the affected bones appeared to be normal, except that the cortex of the femoral midshafts was a little widened.

Pathologic Findings: Necropsy: The body was that of a thin elderly female. There were many yellowish macular lesions in the skin of the face, neck, and extensor aspects of the shoulders. There was a group of similar yellow nodules in the dura along the course of the superior longitudinal sinus. The skull, pituitary, and brain appeared to be normal. A tumor-like mass, of about 1 cm. in diameter, was found in the larynx below the true vocal cords, and there was great mucosal thickening of the entire length of the trachea and main bronchi. The visceral pleurae were studded with yellow nodules which extended into the lung parenchyma to a depth of up to 2.5 cm. The right lung weighed 490 gm., the left, 426 gm. They showed many areas consisting of small, cystlike spaces, the "cysts" measuring 2 to 5 mm. in diameter, and many fibrotic areas. The larger bronchi were not abnormally dilated, and the pulmonary vessels showed little atheroma.

The heart weighed 420 gm. There were yellow deposits beneath the visceral pericardium and the endocardium of both ventricles, especially on the papillary muscles and interventricular septum. The ventricles were moderately hypertrophied and dilated, and the myocardium contained focal deposits varying in size from 0.3 to 1.5 cm. in diameter, and in color from yellow to gray. The valves appeared to be normal, and the coronary vessels showed very little atheroma, and no reduction in their lumina.

Confluent yellow plaques were seen in the intima of the thoracic and abdominal aorta. The vessel was, in its thoracic course, embedded in a dense mass of fibrous tissue.

Some yellow deposits were found in the synovial membrane of the left knee joint.

Histology: *Skin* from the same area of the front of the chest from which a biopsy specimen had been taken in 1949 showed thinning of the epidermis, poor differentiation of the basal layer, and flattening of the rete pegs, while in the dermis there was marked fibrosis but very few foam cells, and no giant cells were present.

The yellow patches seen in the *heart* consisted of lipid deposition and fibrosis in varying proportions. Some areas were composed of a cellular granulation tissue containing many foam cells, fibroblasts, macrophages, lymphocytes and "foreign body" giant cells, others of relatively acellular collagenous fibrous tissue, and between these two extremes were areas of fibrosis of differing degrees of cellularity.

The interventricular septum was heavily involved, the muscle bundles being separated and replaced by fibrous tissue. Some of the smaller coronary vessels showed perivascular fibrosis. Atheromatous changes were very slight.

Myocardium taken from the most severely affected areas contained 3.75% of its dry weight of cholesterol.

The *lungs* showed considerable emphysema, and most of the small bronchi were dilated. The smaller pulmonary arteries showed perivascular fibrosis and some atheroma. Large areas of lung parenchyma were replaced by fibrous tissue, most of which was acellular and densely collagenous. Some of the subpleural deposits were composed of a more cellular granulation tissue, in which foam cells, macrophages, fibroblasts, and giant cells were seen. A specimen of pulmonary tissue contained 0.131% of its dry weight as cholesterol.

The trabecular pattern of the *femur* was far more complex than normal, the osteoid seams being unusually thick and the reduced marrow spaces occupied by a rather loose, acellular fibrous tissue containing small clusters of foam cells. The megakaryocytes, myeloid cells, and erythroid cells were virtually absent (figure 5). The *rib* marrow presented an entirely different picture: the trabecular pattern was normal, and the marrow spaces were occupied by granulocytes, normoblasts, and megakaryocytes in their normal proportions. The eosinophils were not increased in number.

The *spleen* showed no abnormality; there were no foam cells, fibrosis or extramedullary hemopoiesis.

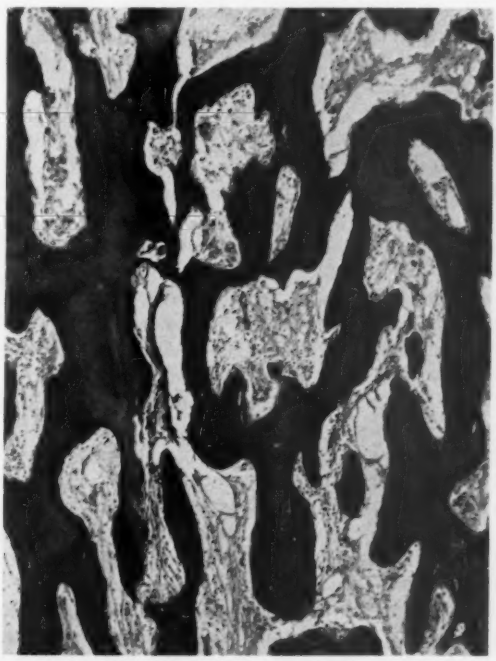

FIG. 5. Femoral bone marrow. Low power. Thickened osteoid seams enclosing reduced marrow spaces, which are filled by fibrous tissue and groups of foam cells.

The *liver* and *kidneys* showed no significant changes. The liver contained 0.27% of its dry weight as cholesterol.

DISCUSSION

The features of this case which are of greatest interest are the lesions in the heart and bone. Xanthomatosis of the normocholesterolemic type has long been known to involve the pericardium, but we have been unable to find any record of similar involvement of the endocardium or myocardium. Thannhauser in 1950[10] considered that such endocardial and myocardial lesions are never found in this type of xanthomatosis.

There seems no reason to doubt that, in the present instance, the extensive implication of the interventricular septum produced the functional abnormalities reflected in the electrocardiogram, for the coronary vessels were only very slightly atheromatous, and there was no evidence of any pathologic change in the myocardium other than xanthomatosis. The usual cause of heart failure in Hand-Schüller-Christian disease and related conditions, in both children and adults, is pulmonary fibrosis.[11] Cystic changes in the lungs are common, the cysts being the result of bronchiolar dilatation.[7] Intimal infiltration of the small pulmonary arteries is thought to be the proximate cause of right heart failure.[1] In our patient, heart failure was chiefly the result of systemic hypertension, although there was a good deal of fibrosis and cyst formation in the lungs. This pulmonary damage, which was doubtless responsible for much of the respiratory embarrassment, was not detected radiologically, the chest films remaining normal in appearance even when the patient was extremely breathless. It seems likely that xanthomatous narrowing of the trachea and bronchi accentuated the attacks of mucus retention which are sometimes associated with tracheostomy.

The classic bony lesion of xanthomatosis appears on the x-ray as a punched-out area, usually in a flat bone. The bones sometimes have a "moth-eaten" appearance on the film,[10] and there may be osteosclerosis,[9] a finding said to be characteristic of the healing phase of the disease.[6] Coarse trabeculation has also been reported.[2] The radiologic appearances in the present case, with patchy sclerosis, disorganized trabeculation, and new bone formation affecting the long bones alone, were those of myelosclerosis of the secondary type.[5]

On microscopic examination, the marrow changes were found in the long bones only, and were more osteosclerotic than myelofibrotic. These two observations indicate that the myelosclerosis is secondary and not primary or "idiopathic" in type, for bone formation of the degree present in this case is a late feature in primary myelosclerosis, and would not be seen in peripheral bones until costal, sternal, and vertebral marrow was affected, at the least by replacement of many marrow spaces by fibrous tissue containing numerous megakaryocytes. Furthermore, the spleen at such an advanced stage of the disease would be considerably enlarged, and would show extramedullary hemopoiesis, with megakaryocytes present in fair number.[3]

The changes in the bones in this case appear to be those of a reaction to the presence of lipid deposits. In the heart, lungs, bronchial tree, and skin the same sequence of events was to be observed: foam cells → granulation tissue → fibrous tissue, and in the marrow this process resulted in abnormal bone formation.

Summary

An account is given of the case of a woman, aged 56 at the time of her death, with normocholesterolemic xanthomatosis. The disease affected the skin, respiratory passages, lung parenchyma, pleurae, pericardium, myocardium, adventitia of great vessels, dura mater, and bone.

Of particular interest were (1) the myocardial lesions, hitherto undescribed in this type of xanthomatosis, which led to arrythmia, and (2) the bone changes, which were those of secondary myelosclerosis.

ACKNOWLEDGMENTS

Material for this case report has been collected from many sources, since the subject of it had been under the observation of several physicians over the years, and we are grateful for permission to quote from their records. We are particularly indebted to Dr. F. B. Wright and Dr. F. Mulcahy for their reports on the x-rays, to Dr. D. E. Anderson for the electrocardiographic report, and to Dr. H. Varley for lipid estimations.

We are obliged to Professor A. C. Campbell for his helpful criticism in the writing of this paper.

SUMMARIO IN INTERLINGUA

Es presentate le historia del caso de un femina de etate medie con xanthomatosis normocholesterolemic. Le remarcabile aspecto del caso es le affection de endocardio, myocardio, e osso.

Le patiente—un inter 13 fraternos e le sol afficite per le condition, in tanto que nos ha potite determinar lo—notava rubiastre placas al latere del collo in le curso del quinte decennio de su vita. Gradualmente le placas deveniva plus numerose e ultimemente coperiva facie, collo, thorace superior, e ambe spaldas. In le curso del tempore illos deveniva confluente, plus obscur, e plus platte. Un massa laryngee necessitava tracheotomia que non succedeva a prevenir progressive dyspnea e cyanosis. In le duo ultime annos del vita le patiente suffreva numerose attaccos de acute edema pulmonar. In un de istos illa moriva, minus que 10 annos post le apparente declaration del morbo. Ante iste disveloppamento, le patiente se habeva trovate in bon stato de sanitate. A parte moderate grados de hypertension, illa suffreva apparentemente solo de xanthomatosis.

Durante le integre periodo de observation, le concentration de cholesterol sanguinee esseva normal, e ante le ultime anno del vita, repetite electrocardiogrammas esseva etiam normal. Sed alora—i.e. durante su ultime anno—defectos de conduction comenciava manifestar se. Radiographias demonstrava le alterationes de myelosclerosis in le terminos del ossos longe.

Al necropsia il esseva constatate que le corde habeva suffrite infiltrationes de depositos de cholesterol e de alterationes fibrotic, iste ultimes particularmente in le septo. Fibrosis del medulla, con spissificate rhaphes osteoide esseva trovate in le ossos longe sed non in le cranio o le costas. Le pulmones e altere tissus monstrava varie grados de deposition de cholesterol, formation de cellulas gigante, e fibrosis. Le vasos coronari non esseva atheromatose.

Es opinate que le deposition de cholesterol in le tissus es sequite ultimemente per fibrosis in ille tissus e que, in le caso de osso, isto causa un typo secundari de myelosclerosis, durante que in le corde le depositos pote esser le causa de dysfunction conductional.

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9. Snapper, I.: Medical clinics on bone diseases, 1943, Interscience Publications, Inc., New York.
10. Thannhauser, S. J.: Lipidoses, 1950, Oxford University Press, New York.
11. Thompson, C. Q., Keegan, J. J., and Dunn, A. D.: Defects of membranous bones, exophthalmos and diabetes insipidus. Report of a case, with necropsy, Arch. Int. Med. **36**: 650, 1925.

EDITORIALS

ON THE REPORTING OF CASES

CAREFUL and intelligent observation of the sick patient lies at the very core of the practice of medicine. From time immemorial physicians have improved their own practice of medicine by noting carefully the manifestations of disease and have assisted their colleagues by communicating the results of their observations. Case reports published in the ANNALS OF INTERNAL MEDICINE have been for many years a valuable and stimulating source of educational material for the medical reader. The new Editor will continue this section. He invites the readers of the ANNALS to continue to submit case reports for publication.

Variety of disease is one of the fascinations of our profession. But not all interesting cases can be written up and not all case reports submitted can be published. The Editor will favor those case reports that exhibit three characteristics: novelty, utility, brevity.

Novelty: There is something new about the case. It is either the first case reported or there have been so few cases reported previously that the disease entity or syndrome is not yet defined. Or some new or very unusual observation or piece of information increases the understanding of a well-known disease. The disease may be old but the news must be new (man bites dog, not dog bites man).

Utility: The information about this case will be useful to other physicians and students of the disease. In a sense all information is useful but some items are more useful than others. Avoid long, uncritical reviews of the literature. Be selective; the verdict of history must await the future but the author and the Editor should attempt to anticipate it as best they may.

Brevity: The case report should be brief, succinct, to the point. This comment is a cry for help from an editor almost drowning in a sea of words. Strongly recommended to would-be authors is that wonderful little book by Strunk and White, *The Elements of Style.** In this volume, E. B. White, in pithy language and humorous style, sets forth the central theme of his old teacher, Professor Strunk: vigorous writing is concise. Do not embrace brevity for brevity's sake, but make every word tell. Omit needless words!

Here, from the pen of the Bard of Avon, is a succinct report of a case of old age:

> "Have you not a moist eye, a dry hand, a yellow cheek, a white beard, a decreasing leg, an increasing belly? Is not your voice broken, your wind short,

* Strunk, W., Jr., and White, E. B.: The Elements of Style, The Macmillan Co., New York, 1959, pp. 71.

your chin double, your wit single, and every part about you blasted with antiquity, and will you yet call yourself young?" *

The patient, of course, is Falstaff, and the words about him are telling! When old age is described in its ultimate physiologic, metabolic, and biochemical terms, may the needless words be as missing and the needed words be as telling.

Our basic form of medical teaching today is built around the case, the patient with a disease. A patient without a disease is a therapeutic goal, a disease without a patient is a mere abstraction. Abstractions may be intellectually satisfying but abstractions are only useful when applied to particulars. In this case the patient is the particular. If there is novelty and utility, be an author; if there is brevity, there may be a reader.

J. R. E.

ON THE NATURE OF CARDIAC CONTROL †‡

THE SURVIVAL and, in a sense, the supremacy of the mammalian class are dependent on biological control mechanisms that render the organism extraordinarily responsive to change. One such control mechanism is that which governs the heart, conferring on it the ability to vary its output and external work between very wide limits in remarkably short periods of time. Some organisms, whose natural environment requires relatively little responsiveness, have no need for complex control systems. Yet no organism high enough in the zoological scale to possess anything resembling a heart is totally unresponsive to change. In no known organism is the heart or its analog set permanently at a given functional level. Unicellular and simple multicellular organisms have no self-contained circulatory control, but some form of cardiac control is known to exist at least as low in the animal kingdom as in the phylum *Annelida*. Many members of the phylum possess closed circulatory systems, including capillary beds, and one of its orders (*Polychaeta*), displays a heart of sorts. This, the most primitive of hearts, is actually nothing more than a thick-walled, rhythmically contractile, expanded portion of the dorsal vessel. The control of the circulation of *Annelida* is not fully understood, although it is known that it can at least vary its pulse rate in response to change in intracardiac (intraluminal) pressure.[1]

Clearly defined cardiac control systems are identifiable in various mem-

* Shakespeare, W.: The Second Part of King Henry the Fourth, Act I, Scene 2.

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‡ Presented at the Basic Medical Science Session of the Annual Meeting of the American College of Physicians, San Francisco, California, April 4, 1960.

[1] Clark, A. J.: Comparative physiology of the heart, 1927, The Macmillan Company, New York.

bers of the phylum *Mollusca*, especially in the cephalopods. In the octopus, for example, the ventricular musculature is capable of producing pressures up to 80 mm. Hg,[2] responds to change in intraventricular pressure, and is equipped with inhibitory nerves.[3]

Arthropods in general have much less advanced circulatory systems than that of the *Mollusca*, but one member of the phylum is of especial interest. It was on *Limulus polyphemus* that Dr. A. J. Carlson did the first thorough study of an integrated cardiac control system. *Limulus* is an arthropod of exceedingly primitive form. Better known as the horseshoe crab, its form and habits are said by zoologists to have endured virtually unchanged for something like 300 million years. This takes it back well before there were any mammals or even birds as we now know them.[4] Just as *Limulus* preceded the mammalian class so it may well outlast it; we, as mammals, seem to have sacrificed durability for adaptability. Be this as it may, *Limulus* suited Carlson's purposes because it grows to comparatively large size, and its primitive, segmented heart sometimes reaches 20 cm. in length when full grown (4 years). In *Limulus*, and in other lower animal forms, Carlson found evidence that the rhythmic beat of the heart is neurogenic and that such animals have inhibitory and excitatory fibers leading to the heart.[3, 5, 6, 7, 8, 9] This, of course, is a description, in simple form, of a complete neural cardiac control mechanism. Three years later, Carlson established that an increase in hydrostatic pressure within the ventricle brought about an increase in amplitude of contraction, and from this observation drew the conclusion that ". . . the augmentation of the strength of the beat is, at least in part, due to a direct action of tension on the heart muscle. . . ." [10] This, in effect, is the other side of the coin, and is the facet of cardiac control that was later embellished and extended by Straub [11] and Starling.[12] In any event, Carlson left the question of cardiac control a great deal more advanced than was the case when he first turned his mind to it,

[2] Fuchs, S.: Beiträge zur Physiologie des Kreislaufes bei den Cephalopoden, Pflügers Arch. f. Physiol. **60**: 173, 1895.

[3] Carlson, A. J.: The physiology of the invertebrate heart, Biol. Bull. (Woods Hole) **8**: 231, 233, 1904–05.

[4] Teale, E. W.: King crab, modern creature of the past. The Illustrated Library of the Natural Sciences, Vol. 2, p. 1338, 1958, Simon & Schuster, New York.

[5] Carlson, A. J.: The rhythm produced in the resting heart of *Mollusca* by the stimulation of cardio-acceleration nerves, Am. J. Physiol. **12**: 55, 1904–05.

[6] Carlson, A. J.: The nervous origin of the heartbeat in *Limulus* and the nervous nature of coördination or conduction in the heart, Am. J. Physiol. **12**: 67, 1904–05.

[7] Carlson, A. J.: The nature of cardiac inhibition with special reference to the heart of *Limulus*, Am. J. Physiol. **13**: 217, 1905.

[8] Carlson, A. J.: Comparative physiology of the invertebrate heart. IV. The physiology of the cardiac nerves in the arthropods, Am. J. Physiol. **15**: 127, 1905–06.

[9] Carlson, A. J.: Comparative physiology of the invertebrate heart. V. The heart rhythm under normal and experimental conditions, Am. J. Physiol. **16**: 47, 1906.

[10] Carlson, A. J.: On the mechanism of the stimulating action of tension on the heart, Am. J. Physiol. **18**: 149, 1907.

[11] Straub, H.: Dynamik des Säugertierherzens, Dtsch. Arch. klin. Med. **115**: 531, 1914.

[12] Starling, E. H.: Linacre Lecture on the Law of the Heart, 1918, Longmans, Green & Co., New York.

and it is a little discouraging to note how clearly he envisaged future difficulties. His comment, published in 1907, is uncomfortably apt 53 years later: "In the intact heart, [the] direct relation between tension and rhythm is obscured through the nervous control of the heart by the central nervous system." [10]

In our own time, Carlson's early work is not often quoted but its influence is not difficult to discern. His work with the hagfish, a very primitive chordate,[13] has recently served as the basis for renewed attacks on the phylogenesis of cardiac control. The hagfish, Carlson tentatively indicated, has an aneural heart which, according to recent workers,[14] does not display the relation between stretch and force of contraction that is so characteristic of all known types of muscle. This suggests that at least one form of life, and a chordate at that, has a heart that is controlled solely by circulating hormones of some kind. Arguing phylogenetically, it seems unlikely that a relatively advanced member of the animal kingdom should possess the most primitive and probably the least effective cardiac control system yet found, especially when *Limulus,* which is actually lower in the animal kingdom than is the hagfish, displays all the main features of the mammalian control system. But the hagfish, as Carlson noted, needs further study. If its heart is truly aneural (and Augustinsson et al.[15] recently confirmed the older work), and if its cardiac muscle is really devoid of the tension-length property common to all other muscle tissue, it is almost certainly in a class by itself. The prospect of working with such an organism may, perhaps, bring cardiovascular physiologists abreast of their renal colleagues who have utilized phylogenetic approaches to excellent advantage.

It was in the amphibian heart that Frank [16] first showed that Blix's and von Kries's work on striated muscle could be applied equally to cardiac muscle; the stretched muscle, within limits, contracts more forcefully than does the unstretched. Starling's work along the same line is too well known and too often quoted to need elaboration beyond noting that he and his successors tended to invest all cardiac control in the tension-length phenomenon. The myogenic component of control systems was supposed to be primary, although the neural component, to do Starling justice, was not entirely ruled out. Even before Starling delivered his Linacre Lecture, however, one important objection to his broadly extended theory was already firmly on the books. The undiluted Starling hypothesis requires that a necessary prelude to increase in ventricular stroke work is increase in end-diastolic

[13] Carlson, A. J.: The presence of cardio-regulative nerves in the lampreys, Am. J. Physiol. **16**: 230, 1906.

[14] Jensen, D.: Personal communication, 1960.

[15] Augustinsson, K.-B., Fange, R., Johnels, A., and Ostlund, E.: Histological, physiological, and biochemical studies on the heart of two cyclostomes, hagfish (*Myxine*) and lamprey (*Lampetera*), J. Physiol. **131**: 257, 1956.

[16] Frank, O.: Zur Dynamic des Herzmuskels. Ztschr. Biol. **32**: 370, 1895. Translated by Chapman, C. B., and Wassermann, E., Am. Heart J. **58**: 282, 467, 1959.

volume. Yet von Anrep[17] had already shown in 1912 that epinephrine causes a *decrease* in end-diastolic volume along with an increase in stroke work. Later work by Liljestrand and co-workers[18] was also not in keeping with the extreme Starling view; they showed that total cardiac (not ventricular) volume is maximal when the human subject is supine and that, with the onset of exercise, it actually diminishes. All this notwithstanding, Starling's Law of the Heart came generally to be accepted as the cardiac control mechanism in the human, possibly because it served as a convenient base for a general theory of cardiovascular function which could cover the failing as well as the compensated heart. When counterreaction finally set in, it did so with telling effect. By the end of World War II, there was a tendency to consider Starling's Law to be a property solely of the isolated heart with little or no applicability to the intact mammal.

Chronologically, one should cite Sarnoff's work as the most significant effort in recent years to rescue Starling's Law from oblivion.[19] He showed, in the open-chested dog, that the heart does respond according to Starling's Law but that it does so from different base levels depending on various circumstances. Hence, we have the Sarnoff "family of ventricular function curves," relating an index to left ventricular end-diastolic volume and to work done in the stroke that immediately follows. The objections to Sarnoff's concept are several: first, the index to end-diastolic volume may be wrong; second, the open-chested dog is perhaps not comparable to the intact animal. Most important of all, the concept is so fluid and so supple that one can use it to explain almost any set of functional data, and there is the danger that, by shifting from curve to curve and from instant to instant, more confusion than enlightenment may result. The Sarnoff work, however, has stood up remarkably well and has served to stimulate a reappraisal, rather than a summary rejection, of the entire Starling view. Sarnoff's experimental design, however, did not permit him to measure the necessary variables directly and under physiologic conditions. Rushmer's approach, using intact unanesthetized dogs and an ingenious method of following change in various left ventricular diameters in lieu of volume,[20] stimulated a great deal of interest but neither affirmed nor denied Sarnoff's view. Rushmer himself gradually came to the conclusion that the Starling principle, requiring increased return of blood to the ventricle as the chief initiating mechanism for increase in stroke work, is largely invalid. More recently, he has reviewed a large number of exercise studies in human

[17] von Anrep, G.: On the part played by the suprarenals in the normal vascular reactions of the body, J. Physiol. **45**: 307, 1912.

[18] Liljestrand, G., Lysholm, E., and Nylin, G.: The immediate effects of muscular work on the stroke and heart output in man, Skand. Arch. Physiol. **80**: 265, 1938.

[19] Sarnoff, S., and Berglund, E.: Ventricular function. I. Starling's Law of the Heart studied by means of simultaneous right and left ventricular function curves in the dog, Circulation **9**: 706, 1954.

[20] Rushmer, R. F.: Continuous measurements of left ventricular dimensions in intact, unanesthetized dogs, Circulation Res. **2**: 14, 1954.

subjects, and reports on this basis that the increase in stroke volume plays little or no role in human adaptation to exercise, the important factor being increase in rate.[21] This, if true, would be powerful support for the primacy of a neural control mechanism in human beings and would virtually eliminate a myogenic factor which, in fact, is the basis of Starling's Law.

Our own interest in the area was kindled some years ago when we realized—or had it pointed out to us—that no real answer to the questions concerning the nature of cardiac control in intact mammals would be forthcoming until one could actually measure ventricular volume. For this reason we set out, in 1956, to adapt the biplane cinefluorographic technic to the measurement of left ventricular volume. The technic, as worked out in collaboration with Dr. Orland Baker, has many drawbacks, the most formidable of which is its tediousness.[22] Thirty-five millimeter films, taken at 30 frames per second, record the passage of radiopaque medium through the left ventricle and are used to trace the contours of the chamber at intervals of 1/30 second through six or eight cycles. Because the views are at a 90° angle to each other (LAO and RAO), major and minor diameters of the ventricular cavity can be obtained. On the assumption that the cross-section of the left ventricle is roughly circular or oval, the two diameters are then used to calculate an area. Diameters are measured at one millimeter intervals from top to bottom of the ventricular cavity and, in effect, the volumes of many one millimeter slices are calculated and summed. The end result of all this is a value for ventricular volume measured every thirtieth of a second, from a series of which one can construct ventricular volume curves. Dr. Baker's ingenuity led us to construct adjunct equipment which vastly facilitates the operation. We still must trace ventricular contours from each pair of frames by hand, but the real labor (measurement of diameters and calculation of areas) is now done by a scanner-computer. This instrument accepts long series of paired tracings on roller paper, measures diameters from top to bottom at one millimeter intervals, and calculates volume for us. It does in 20 minutes what two technicians with calculators once needed three weeks to accomplish. From such films one can also measure aortic diameters just above the aortic bulb, from which aortic cross-sectional area can be calculated. It is not possible, unfortunately, to measure the diameters of the aortic valvular orifice itself but, using the data that are available, one can approximate an aortic velocity curve. From all these data, and using simultaneously recorded pressure curves, complete integrated stroke work calculations are approachable.

This rather complex research tool permitted us to study the effects of mild exercise on left ventricular stroke volume and stroke work in the intact

[21] Rushmer, R. F.: Constancy of stroke volume in ventricular response to exertion, Am. J. Physiol. **196**: 745, 1959.

[22] Chapman, C. B., Baker, O., Reynolds, J., and Bonte, F. J.: Use of biplane cinefluorography for measurement of ventricular volume, Circulation **18**: 1105, 1958.

anesthetized dog.[23] The animals were suspended before the cameras and, after resting films were run off, rhythmic galvanic stimuli were applied to the muscles of the hind quarters for about 10 minutes. The exercise was of sufficient intensity to increase oxygen intake to about three times that of the resting value. Another set of films was then made at the end of the period of exercise. These studies show quite clearly that end-diastolic volume usually decreases during exercise, although stroke work is ordinarily increased. Stroke volume also usually rises, although at such low levels of exercise the amount of increase is small. Adaptation to exercise under these circumstances is, therefore, not simply a matter of increase in rate. On the other hand, the unmodified Starling hypothesis cannot hold, since end-diastolic volume decreases at a time when stroke volume is increased. Increase in return of blood to the ventricle cannot, therefore, product increase in stroke volume and stroke work by increasing end-diastolic fiber length over the resting value, as required by Starling's Law. Plotting end-diastolic volume against stroke work at rest and during exercise shows the resting values grouped in the lower right corner of the plot and the exercising values grouped toward the upper left corner. If the Starling relationship holds under the circumstances, it may mean that something like Sarnoff's "family of curves" is biological fact, i.e., one curve applies to the resting values and another curve, lying above and to the left, applies to the exercising ones. This is, of course, supposition. Our method does not permit us to plot function curves of the sort Sarnoff obtains. All we can say is that we obtain a resting point and an exercising point that may lie on two different curves of the Sarnoff type. If, however, one compares end-diastolic volume with stroke work in a series of beats under resting conditions, a clear relation between the two usually emerges. This relation is as Starling described it: as end-diastolic volume rises, so does stroke work We therefore found it impossible to discard the Starling hypothesis altogether but began to regard his formulation, at least as it concerns response to exercise, as overextended and perhaps incomplete.

Meanwhile another experimental approach directed our attention to Rushmer's contention that stroke volume plays little or no role in response to exercise. The work done in dogs involved low levels of exercise and the demonstrated increase in stroke volume, though definite, was quite small; in a few instances it was entirely absent. We therefore turned to work done in our laboratory on human subjects as described by Mitchell, Sproule, and myself.[24] The studies involved very heavy exercise loads, producing oxygen intakes that were about 10 times those recorded at rest, and causing cardiac output to rise to about five times the resting output (dye dilution method). In all such subjects stroke volume, as calculated by dividing

[23] Chapman, C. B., Baker, O., and Mitchell, J. H.: Left ventricular function at rest and during exercise, J. Clin. Invest. **38**: 1202, 1959.

[24] Mitchell, J. H., Sproule, B. J., and Chapman, C. B.: The physiological meaning of the maximal oxygen intake test, J. Clin. Invest. **37**: 538, 1958.

cardiac output by pulse rate, at heavy exercise loads was about double that obtained at rest in the standing position. Subsequently, as reported by Fisher and Sproule,[25] we determined the effect of using resting supine (instead of standing) values for stroke volume as our base line. These values, of course, are considerably higher than those obtained during quiet standing. It was found that no matter what base line is used, there is a significant increase in stroke volume during heavy exercise, and we believe it fair to say that the normal human subject cannot attain maximal oxygen intake without utilizing increase in stroke volume along with increase in pulse rate and in A-V oxygen difference. Here again is evidence that some form of intrinsic ventricular reactivity must play a role in cardiac adaptation to stress, whether or not one is willing to apply the term "Starling's Law" to such reactivity.

It is obviously dangerous to attempt to combine two pieces of evidence of the sort just presented for theoretical purposes: one applies to anesthetized dogs at low levels of exercise in which stroke volume is measured directly; the other applies to unanesthetized human subjects exercising at increasing levels of exercise, stroke volume being obtained by dividing cardiac output by pulse rate. Yet a connection between the two is suggested by the work of Liljestrand and co-workers,[18] quoted earlier. It showed that total heart volume is maximal when the subject is recumbent and resting. Stroke volume at the same time is high but not maximal. Both heart volume and stroke volume decline when the subject is placed in the sitting position (still resting), and both increase with increasing exercise loads. Total heart volume, however, did not reach the level seen in the recumbent resting subject, but stroke volume considerably exceeded the value seen under such conditions. A possible explanation is that the decrease in total heart volume, and in the canine end-diastolic left ventricular volume, noted at low levels of exercise, is a manifestation of alteration in ventricular function, so that for any given end-diastolic volume, contractility is higher and a greater stroke volume is achieved. This implies that residual volume, like end-diastolic volume, declines in the transition from a state of rest to light exercise. Thereafter, as exercise loads become heavier, end-diastolic volume begins to increase and with it the force of contraction also increases as provided by Starling's Law. Residual volume, expressed as per cent of end-diastolic volume, should decline very little as exercise loads increase, although some further decline might be expected as maximal exercise loads are approached. Teleologically, this view is attractive in that it limits the dilatation that would be necessary at heavy exercise loads; it also fits reasonably well with experimental findings and suggests that the organism, stressed at or near maximal levels, utilizes all of the known components of the cardiac control system.

[25] Chapman, C. B., Fisher, J. N., and Sproule, B. J.: The behavior of stroke volume at rest and during exercise in human beings, J. Clin. Invest. 39: 1208, 1960.

Critical denervation experiments also suggested that myogenic factors are involved in response to exercise.[26] In these experiments, done with Drs. Tom Bruce and J. N. Fisher, resting studies on the intact dog were carried out first. Then unilateral sympathectomy from the middle cervical ganglion to the fifth thoracic ganglion was done. A week later, sympathectomy on the other side was done and the dog was allowed to recover fully. The last step was to measure left ventricular response at rest and during exercise, before and after bilateral vagal section in the sympathectomized dog. These studies allowed us to examine the effect of sympathectomy alone and of complete cardiac denervation in response to exercise. The effect of vagal section alone was studied in other experiments on different dogs. It caused marked resting tachycardia but there was still a modest increase in both pulse rate and stroke volume during exercise. Sympathectomy alone caused some fall in resting rate but, again, exercise produced increase in both pulse rate and stroke volume. Total denervation removed the rate response entirely. This was 125 at rest and did not change significantly during exercise. Stroke volume, however, rose about 21% over the resting figure, and the cardiac response to exercise, as judged by increase in minute volume or minute work, was quite respectable. The denervated heart in the otherwise intact dog, therefore, is still able to respond to exercise and it does it solely by means of a myogenic factor.

The final question, and probably the most important, is this: How, in denervated dogs, is this myogenic response to stress mediated? One obvious possibility is that exercise induces adrenal medullary outflow which, in turn, produces increased ventricular response via circulating hormones of the sympathomimetic type. The difficulty with this hypothesis is that the direct effect of catechol amines on the ventricles is well documented; they induce the heart to beat faster and usually cause a diminution in end-diastolic volume along with increased force of contraction. Neither an increase in pulse rate nor a decrease in end-diastolic volume was observed during exercise in the denervated dogs. The other possibility is that the denervated heart in otherwise intact dogs reacts more or less precisely like the heart in the original Starling isolated heart preparation, and that an increase in return of blood to the ventricle is the factor that initiates an increase in stroke volume and stroke work. The fact that end-diastolic volume in the denervated animal increases during exercise, instead of decreasing as it usually does in normal dogs, supports this view.

It is now crucial to observe, as meticulously as possible, the changes that take place at the very beginning of exercise, something which is very difficult to do with our technic and which we have not yet attempted. We can say, however, that buried within the group of mechanisms responsible for cardiac

[26] Chapman, C. B., Bruce, T., Baker, O., and Fisher, J. N.: The effect of partial and total denervation of the heart on left ventricular function, abstract *in* J. Clin. Invest. 39: 966, 1960.

control in the mammal is a definite myogenic factor, however it is mediated. Whether this is the same as saying that Starling's Law applies to the intact mammal or not depends somewhat on what one considers Starling to have included in his formulation. Obviously his original concept, borrowed from Otto Frank, has merit although many of the generalizations he later drew from the original work can no longer be supported.

In conclusion, if one must have a unifying theory, the least noxious and most easily supported seems to be as follows: a fundamental feature and, perhaps, a sort of final common pathway of the mammalian cardiac control system is intrinsic myocardial reactivity. On this fundamental feature neural inhibitory and accelerator influences impinge, the former acting primarily to decrease rate and the latter to increase rate and ventricular reactivity. At low levels of stress, increase in rate is preferred to increased force of contraction. At higher levels, both mechanisms play an integrated role.

CARLETON B. CHAPMAN

BOOK REVIEWS

Arthritis and Allied Conditions: A Textbook of Rheumatology. 6th Ed. Editor: Joseph Lee Hollander, M.D. Section Editors: Edward W. Boland, M.D., Richard H. Freyberg, M.D., Wallace Graham, M.D., John Lansbury, M.D., Currier McEwen, M.D., Charles Ragan, M.D., William D. Robinson, M.D. and Charley J. Smyth, M.D. 1,306 pages; 24 × 16 cm. Lea & Febiger, Philadelphia. 1960. Cloth-bound. Price, $20.00.

This excellent book is the sixth edition of Comroe's *Arthritis and Allied Conditions,* published initially in 1940. Extensive changes and revisions have been made since the fifth edition was published in 1954. Nineteen new chapters have been added, including the Study of Connective Tissue, The Rheumatoid Factor, The L. E. Phenomenon, Stress and the Rheumatic Diseases, Immunology in Rheumatic Diseases, Polyarteritis, Dermatomyositis, Alkaptonuria and Ochronosis, Metabolic Bone Disease, Amyloidosis, Arthritis from Disorders of the Blood Formation, Neurogenic Arthropathy, and Congenital Disorders of Bone and Joints. The book has also gained considerably by the addition of 119 new illustrations. The reproduction of some of the roentgen pictures, unfortunately, is not of the high standard that this outstanding book would demand.

The section on "Rheumatoid Arthritis" occupies, as it has in prior editions, the largest part of the book. Many of the chapters have been reorganized and rewritten. A special chapter is concerned with the use of synthetic steroids.

The list of contributors and section editors contains the names of leading authorities in the fields of arthritis and rheumatology. Their particular experience is condensed into comprehensive reviews that include extensive bibliographies. The book is recommended, not only for rheumatologists, but as a valuable source of information for internists, researchers, orthopedic surgeons, and graduate students.

Adalbert F. Schubart, M.D.

Diagnosis and Treatment of Tumors of the Chest. Edited by David M. Spain, M.D. 371 pages; 18 × 26 cm. Grune & Stratton, Inc., New York. 1960. Price, $14.75.

Sponsored by the American College of Chest Physicians, edited by Dr. Spain, and written by men of competence in their fields, this book is a superb presentation of the subject of chest tumors. It begins with a detailed and lucid presentation of available data on the causation of bronchogenic carcinoma, including a consideration of the pathology and natural history of this disease, and then takes up its diagnosis and management. The section on the difficult subject of radiotherapy is particularly well done and succeeds in presenting a clear picture of indications, objectives, and methods.

All tumors of the chest, including those of mediastinum, esophagus, heart and pericardium, diaphragm and pleura are presented. The illustrations for the section on tumors of the heart and pericardium are outstanding.

The volume is well illustrated throughout and the reproductions, particularly of histologic material, are excellent.

The book should be of great interest and value to any physician concerned with diseases of the chest.

Patrick B. Storey, M.D.

Disease and the Advancement of Basic Science. Edited by HENRY K. BEECHER, M.D. 416 pages; 24 × 16 cm. Harvard University Press, Cambridge. 1960. Price, $12.50.

Twenty-one eminent scientists, most of them clinicians, were given the task of delineating the contributions made by medicine to basic science, a side of the coin less often seen. The resulting series of lectures, here published in book form, accomplished the mission with varying degrees of conviction. Dr. Moore, by contrasting the results of the anatomical studies of da Vinci with those of Vesalius, would have us believe that "basic" research assumes significance only when coupled with "applied." However, most of us would agree that either type of research may lead quite naturally to the other, and to argue about the contributive value of one versus the other seems rather trivial. As cogently put by Dr. Churchill, "the surgeon may also act as a scientist," although to Dr. Bailey the psychiatrist rarely does so.

Despite the dubiety of the device used for the common theme, the book is excellent reading, from the extremely erudite discussion of Dr. Castle to the delightful span of ideas presented by Dr. Gerard. For any individual reader there are bound to be preferences; for me the several contributors who developed the historic growth of the field were most successful, e.g., the essays of Drs. Bearn and Enders being a minor masterpiece. The straightforward reviews of Drs. Weiss, Talbott, Richards, Bauer, and Aub all make good reading, and Dr. Beecher's contribution seemed most stimulating in opening up avenues for fundamental research in an area fraught with almost as many fads and fancies as Dr. Bailey indicated exist in psychiatry.

It was noteworthy that in this philosophical age of the "irrational" man several of these authors discussed the current limitations of the scientific or pseudo-scientific approach to all problems of mankind. The words of Drs. Pauling, Bailey, and Dubos will certainly not be universally received with favor; they are, however, thoughtful men, willing and able with reason and conviction to question the role of measurement (or scientific method) in reaching full understanding of man and his environment. It is unfortunate, perhaps, that for the opening chapter Dr. Pauling did not speak with more authority, but Dr. Dubos's concluding remarks eloquently completed the warning.

WILLIAM D. BLAKE, M.D.

Body Fluids in Surgery. 2nd Ed. By A. W. WILKINSON, Ch.M., F.R.C.S.E., F.R.C.S. 276 pages; 22.5 × 14.5 cm. The Williams and Wilkins Company, Baltimore, Maryland, exclusive U. S. agents. 1960. Price, $5.00.

The usual volume on "body fluids" requires frequent rereading in order to assimilate the mass of numerical and chemical data which are presented, often in a colorless and uninteresting style. This volume too requires rereading, but in this instance, because the process is so pleasant, the factual material seems to slip through one's intellectual fingers. This is due partly to the author's technic and partly to a less intensive pursuit of theory in favor of emphasis on actual patient management. This accent on treatment is so thorough that several pages are devoted to the technics of intravenous infusion.

The American reader may be disturbed by references to "black treacle" as the richest natural source of potassium, or to the use of tea in the treatment of the victim of a crushing injury. Less obvious but more important is the author's frequent recommendation of "an infusion of dextran" and his devotion of twelve pages to plasma substitutes (expanders). Three paragraphs concerned with elective hypotension and hypothermia add to the reader's impression that this new edition has not been as extensively revised as is necessary for publication in 1960.

The de-emphasis of theory and laboratory data in favor of a more clinical approach will be a disappointment to some, but such detailed facts are available else-

where, if desired. The style, the balance between theory and practice, the accent on treatment, and the pleasing organization and format of *Body Fluids in Surgery* will make it a welcome addition to the library of medical students, residents, and practicing surgeons. The scope of the book is ideal for use as a guide in clinical practice, but is entirely too superficial for those teaching surgery. The chapter specifically concerned with infants and children is a significant addition to any book written for the modern student of surgery.

ROBERT M. N. CROSBY, M.D.

The Human Lung. By HEINRICH VON HAYEK, M.D., Ph.D.; translated by VERNON E. KRAHL, Ph.D. 372 pages; 25.5 × 17 cm. Hafner Publishing Company, Inc., New York, 1960. Price, $13.50.

The human lung contains several interrelated but autonomous circulations. Each of these circuits has its own structural features, which are maintained in proper anatomic juxtaposition by the architectural matrix of the lung. The thoracic bellows, composed of the skeleton, the diaphragm, the intercostal and intrathoracic muscles, provides the mechanism for driving the lung and producing ventilation. Dr. von Hayek has constructed a monograph in which each element of this complex system is exhaustively analyzed.

The book opens with a brief, pertinent discussion of tension and pressure relationships of the lung and thorax. Description of the anatomic and functional features of the thoracic cage, diaphragm, and pleura follow. The general structure of the lung and its variations in different zones of the thorax are considered. Descriptions of gross and microscopic anatomy of air passages are exceedingly detailed. A great deal of emphasis is accorded supporting and connective tissues of the airways. The configuration of bronchial musculature is discussed, especially with regard to bronchial shortening and narrowing. There is an analysis of intimate anatomic features of terminal bronchioles and alveolar structures, and their relationships to connective tissue components and pulmonary vessels. About one third of the text deals with the pulmonary and bronchial vascular systems, lymphatics, and nerves. A small addendum, depicting electron microscopic studies of lung, has been included in this edition. More than 270 strategically located illustrations amplify or clarify the text.

An extensive bibliography is subdivided into sections corresponding to chapter headings and subtopics. The index includes references to text and illustrations.

This is a very impressive piece of work. A major effort has been made to provide comprehensive coverage of subjects considered in the text. Where conflicts exist, evidence in support of both viewpoints is presented. Pertinent information, obtained from experimental nonhuman material, is cited when indicated to support a thesis or arbitrate a controversy. The tone set in the opening chapter relating anatomic structure to function of the lung is followed throughout. Anatomic features are discussed in the light of human pulmonary physiologic principles. This vast amount of critically analyzed, detailed information can be used with great benefit by anatomists, physiologists, or clinicians to gain insight into anatomico-physiologic relations of the lung.

Dr. Vernon Krahl, an eminent anatomist and student of the lung, has performed a tremendous task in translating von Hayek's work. The high level of scholarship in the original monograph is the result of von Hayek's study and thought. The clarity of expression and organization in translation demonstrate the empathy which exists between author and translator. Dr. Krahl has pursued his subject with insight and respect. We owe a debt of gratitude to both of these men who are students of the anatomic and physiologic properties of the human lung.

JEROME E. COHN, M.D.

Recent Advances in Cardiology. 5th Ed. By TERENCE EAST, M.A., D.M., F.R.C.P., Physician, and Physician-in-charge of Cardiology Department, King's College Hospital; and CURTIS BAIN, M.C., D.M., F.R.C.P., Consulting Physician, Harrogate General Hospital. 421 pages; 21 × 14 cm. Little, Brown & Company, Boston. 1959. Price, $10.00.

This is the fifth edition of *Recent Advances in Cardiology,* which was originally published in 1929. As the authors state, the dramatic advances in the field of Cardiology have necessitated complete rewriting of the book and the inclusion of a number of new illustrations. Increased emphasis is given the subject of congenital cardiac defects.

The illustrations are of uniformly high quality and are clearly presented. Adequate references follow each discussion. It is not the attempt of the authors to present the reader with a textbook covering the entire field of Cardiology, but rather to present him with recent advances in a succinct and practical way. In this attempt, they have succeeded. However, for a fuller knowledge of the field, the reader would have to consult more detailed textbooks of Cardiology, of which they are many excellent ones available.

LEONARD SCHERLIS, M.D.

The Heart in Industry. By Twenty-four Authors. Editor: LEON J. WARSHAW, M.D., F.A.C.P.; foreword by IRVING S. WRIGHT, M.D. 677 pages; 24 × 16.5 cm. Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, New York. 1960. Price, $16.00.

This work could accomplish more for "the cardiac in industry" than all the Heart Association committees designed to define, elucidate, and correct the problems of employment of individuals with heart disease. The rehabilitative movement will be greatly boosted by the philosophy and concern herein displayed, which will be of great interest also to the laity, to those of other professional disciplines, and to all physicians. Members of cardiac rehabilitation units will attest to the need and desire of every physician to avail himself of the information this extensive work provides.

The authors have an imposing experience in this area, for which there appears to be no substitute. No area or problem of concern has been avoided. Of particular interest is the physician's interpretation of Workmen's Compensation laws as applied to workers with heart disease. The industrial physician's interpretation of his role is well stated and may be better appreciated by the reader. The various types of work are discussed, and the physiologic, psychiatric, and stress aspects of employment in relation to workers with heart disease are authoritatively considered.

Those interested in formal cardiac rehabilitation will find this book an exciting and welcome addition to their resources. It is highly recommended to the industrial physician. Every physician will benefit from this authoritative approach to optimal rehabilitation of his many cardiac patients.

AUBREY D. RICHARDSON, M.D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. So far as is practicable, those of special interest will be selected for review later, but it is not possible to discuss them all.

Academy of Medical Sciences of the USSR: History and Organization, 1944–1959. Prepared in the National Library of Medicine for the Russian Scientific Library of Medicine for the Russian Scientific Translation Program, Public Health Service. Public Health Service Publication No. 702. Public Health Monograph

No. 63. By GALINA V. ZARECHNAK, Ph.D. 48 pages; 26 × 20 cm. (paper-bound). 1960. May be ordered from the U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C.

Administration of the Public Psychiatric Hospital. Report No. 46, July, 1960. Formulated by THE COMMITTEE ON HOSPITALS, GROUP FOR THE ADVANCEMENT OF PSYCHIATRY. 199 pages; 23 × 15.5 cm. (paper-bound). 1960. Published by the Group for the Advancement of Psychiatry, Publications Office, 104 E. 25th Street, New York 10, N. Y. Price, $1.00 (quantity rates on request).

Atlas of Exfoliative Cytology. Supplement 2. By GEORGE N. PAPANICOLAOU, M.D., Ph.D. 94 pages; 23 × 20.5 cm. (unbound pages for insertion in *Atlas*). Published for The Commonwealth Fund by Harvard University Press, Cambridge, Mass., 1960.

Biochemical Values in Clinical Medicine. The Results Following Pathological or Physiological Change. By ROBERT DUNCAN EASTHAM, B.A., M.D. Publisher: John Wright & Sons, Ltd., Bristol, 1960. Available in U. S. A. through The Williams & Wilkins Company, Baltimore. 144 pages. Price, $3.75.

Cerebral Palsy and Related Disorders: A Developmental Approach to Dysfunction. By ERIC DENHOFF, M.D., and ISABEL PICK ROBINAULT, Ph.D. 421 pages; 24 × 16 cm. 1960. McGraw-Hill Book Company, Inc., New York. Price, $12.00.

The Chemistry and Biology of Sialic Acids and Related Substances. By A. GOTTSCHALK. Cambridge University Press, New York. 115 pages. 1960. Price, $4.50.

Clinical Applications of Bronchology. By DEZSO KASSAY, M.D., foreword by CHEVALIER L. JACKSON, M.D. The Blakiston Division of McGraw Hill Book Company, Inc., New York. 225 pages; 24 × 16 cm. 1960. Price, $15.00.

A Clinical Prospect of the Cancer Problem. Neoplastic Disease at Various Sites. By D. W. SMITHERS, M.D., F.R.C.P., F.F.R. E. & S. Livingstone, Ltd., Edinburgh and London, 1960. 232 pages; Price, $8.50.

Diabetic Care in Pictures: Simplified Statements with Illustrations Prepared for the Use of the Patient. 3rd Ed. By HELEN ROSENTHAL, B.S., and JOSEPH ROSENTHAL, M.D. 237 pages; 24 × 15.5 cm. 1960. J. B. Lippincott Company, Philadelphia. Price, $4.50.

Differential Diagnosis of Yaws. By C. J. HACKETT, M.D. and L. J. A. LOEWENTHAL, M.D. World Health Organization Monograph #45. 1960. Geneva, Switzerland. 88 pages. Price, $3.25.

Endogenous Endocrinotherapy, Including the Causal Treatment of Cancer. A Compendium. 11th Ed. By JULES SAMUELS, Amsterdam. 554 pages. 1960. N. V. Cycloscoop, Amsterdam.

The Dispensatory of the United States, 1960 Ed., Vol. Two, New Drug Developments Volume. By ARTHUR OSOL, Ph.G., B.S., M.S., Ph.D., and ROBERTSON PRATT, A.B., Ph.D., with four other coauthors. 240 pages; 27 × 18.5 cm. 1960. J. B. Lippincott Company, Philadelphia. Price, $9.00.

Enzymes in Clinical Medicine. By IRVING INNERFIELD, M.D. 334 pages; 22 × 14.5 cm. 1960. The Blakiston Division of McGraw-Hill Book Company, Inc., New York. $11.50.

Eye Signs in General Disease. By HERBERT HAESSLER, M.D. 1960. 118 pages. Charles C Thomas, Springfield, Ill. Price, $5.75.

Lipids and the Steroid Hormones in Clinical Medicine: Proceedings of an Applied Seminar of the Association of Clinical Scientists. Edited by F. WILLIAM SUNDERMAN, M.D., Ph.D., Sc.D., and F. WILLIAM SUNDERMAN, JR., M.D. 207 pages; 26.5 × 18.5 cm. 1960. J. B. Lippincott Company, Philadelphia. Price, $10.75.

The Liver and Cancer—A New Cancer Theory. 2nd Ed. By KASPER BLOND, M.D. Published by John Wright & Sons, Ltd., Bristol; available in the United States through The Williams & Wilkins Co., Baltimore. 379 pages. 1960. Price, $8.00.

Meaning and Methods of Diagnosis in Clinical Psychiatry. By THOMAS A. LOFTUS, M.D. 169 pages; 24 × 15.5 cm. 1960. Lea & Febiger, Philadelphia. Price, $5.00.

Medical History-Taking. By IAN STEVENSON, M.D. 273 pages; 24 × 16 cm. 1960. Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, New York. Price, $6.50.

The Modern Treatment of Asthma with Special Reference to Gold Therapy. 2nd Ed. By L. BANSZKY. Published by John Wright & Sons, Ltd., Bristol; available in the United States through The Williams & Wilkins Co., Baltimore. 175 pages. 1960. Price, $5.00.

Obstetrics (from the original text of Joseph B. DeLee, M.D.). 12th Ed. By J. P. GREENHILL, M.D., F.A.C.S., F.I.C.S. (Hon.). 1,098 pages; 26 × 18.5 cm. 1960. W. B. Saunders Company, Philadelphia. Price, $17.00.

Occupational Diseases and Industrial Medicine. By RUTHERFORD T. JOHNSTONE, M.D. and SEWARD E. MILLER, M.D. 482 pages; 25.5 × 16.5 cm. 1960. W. B. Saunders Company, Philadelphia. Price, $12.00.

Surgery in the Aged. Editors: FRANK GLENN, M.D., Lewis Atterbury Stimson Professor of Surgery, Cornell University Medical College, etc.; S. W. MOORE, M.D., Professor of Clinical Surgery, Cornell University Medical College, etc.; and JOHN M. BEAL, M.D., Associate Professor of Clinical Surgery, Cornell University Medical College, etc. 534 pages; 26 × 19 cm. 1960. The Blakiston Division, McGraw-Hill Book Company, Inc., New York. Price, $17.50.

Therapeutic Meal Plans: A New Diet Manual. Revised Edition. Prepared by THE DEPARTMENT OF DIETETICS AND NUTRITION, THE UNIVERSITY OF KANSAS SCHOOL OF MEDICINE; revised edition edited by RUTH GORDON, ARLENE PAYNE and HAZEL PARRY. 66 pages; 21 × 13.5 cm. (paper-bound, loose-leaf). 1960. The University of Kansas Press, Lawrence, Kansas. Price, $3.00.

The Year Book of Cancer (1959–1960 Year Book Series). Compiled and edited by RANDOLPH LEE CLARK, JR., B.S., M.D., M.Sc. (Surgery), D.Sc. (Hon.), Houston, Texas, Director and Surgeon-in-Chief, The University of Texas M. D. Anderson Hospital and Tumor Institute, etc.; and RUSSELL W. CUMLEY, B.A., M.A., Ph.D., Houston, Texas, Director of Publications, The University of Texas M. D. Anderson Hospital and Tumor Institute, etc. 533 pages; 20 × 13.5 cm. 1960. The Year Book Publishers, Chicago. Price, $8.50.

Yoga: A Scientific Evaluation. By KOVOOR T. BEHANAN, Ph.D. 270 pages; 20.5 × 13.5 cm. (paper-bound). 1960. Dover Publications, Inc., New York. Price, $1.65.

SPECIAL ANNOUNCEMENT TO SUBSCRIBERS

An extra and seventh number of this volume, Volume 53, of the ANNALS will be published and mailed within a few weeks. This Number 7 will contain the Thirteenth Annual Review of Rheumatism and Arthritis.

MEDICAL NEWS

Meetings

Jan. 6–7, 1961	American Federation for Clinical Research—Eastern Section, Clinical Ctr., NIH, Bethesda, Md.
Jan. 7, 1961	Northwest Society for Clinical Research, Hotel Georgia, Vancouver, B. C., Canada, Jan. 7. Dr. John R. Hogness, University Hospital, Seattle, Secretary-Treasurer.
Jan. 9–12, 1961	White House Conference on Aging—Theme: "Aging with a Future—Every Citizen's Concern," Washington, D. C.
Jan. 19–21, 1961	American Federation for Clinical Research—Southern Section, Jung Hotel, New Orleans, La.
Jan. 19–21, 1961	Royal College of Physicians and Surgeons of Canada—Annual Mtg., Chateau Laurier Hotel, Ottawa, Ont., Canada.
Feb. 4–7, 1961	Congress on Medical Education and Licensure, Palmer House, Chicago, Feb. 4–7. For Information write Mrs. Ann Tipner, A. M. A., 535 N. Dearborn St., Chicago 10.
Feb. 6–8, 1961	American Academy of Allergy, Statler-Hilton Hotel, Washington, D. C., Feb. 6–8. Mr. James O. Kelley, 756 N. Milwaukee St., Milwaukee, 2, Wis., Executive Secretary.
Feb. 6–10, 1961	British Medical Association—Annual Mtg., Aukland, New Zealand.
Feb. 7, 1961	World Health Organization—14th Assembly, New Delhi, India.
Feb. 8–11, 1961	American College of Radiology, Drake Hotel, Chicago, Feb. 8–11. William C. Stronach, LL.B., 20 N. Wacker Drive, Chicago 6, Executive Director.
Mar. 12–17, 1961	American College of Allergists, Statler Hilton, Dallas, Texas, Mar. 12–17. Dr. Howard G. Rapaport, 16 E. 79th St., New York City, Secretary.
Mar. 13–16, 1961	National Health Council, National Health Forum, "Health and Communication," Waldorf-Astoria, New York City, Mar. 13–16. Mr. Philip E. Ryan, 1790 Broadway, New York 19, Executive Director.
Apr. 10–12, 1961	American Academy of Pediatrics, spring meeting, Sheraton-Park Hotel, Washington, D. C., Apr. 10–12. For information write Dr. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill., Executive Director.
Apr. 26–29, 1961	American College Health Association, Detroit, Apr. 26–29. Dr. Norman S. Moore, Cornell University, Gannett Clinic, Ithaca, N. Y., Secretary-Treasurer.

Apr. 27–28, 1961	EASTERN STATES HEALTH EDUCATION CONFERENCE, New York Academy of Medicine, Apr. 27–28. For information write Dr. Iago Galdston, New York Academy of Medicine, 2 E. 103 St., New York City.
Apr. 30, 1961	AMERICAN FEDERATION FOR CLINICAL RESEARCH, Haddon Hall, Atlantic City, Apr. 30. James E. Bryan, 250 W. 57th St., New York 19, Executive Secretary.
Apr. 30–May 1, 1961	AMERICAN SOCIETY FOR CLINICAL INVESTIGATION, Atlantic City, N. J., Steel Pier.
May 2–3, 1961	ASSOCIATION OF AMERICAN PHYSICIANS, Chalfonte-Haddon Hall, Atlantic City, May 2–3. Dr. Paul B. Beeson, Yale University School of Medicine, New Haven 11, Conn., Secretary.
May 1–4, 1961	NATIONAL GERIATRICS SOCIETY, San Francisco, Calif., St. Francis Hotel.
May 4–6, 1961	STUDENT AMERICAN MEDICAL ASSOCIATION, Chicago, Ill., Pick-Congress Hotel.
May 5–7, 1961	AMERICAN SOCIETY OF INTERNAL MEDICINE, Miami Beach, Fla., Eden Roc Hotel.
May 8–12, 1961	AMERICAN COLLEGE OF PHYICIANS—Annual Session, Americana Hotel, Miami Beach, Fla.
May 8–11, 1961	AMERICAN PSYCHIATRIC ASSOCIATION, Chicago, Ill., Morrison Hotel.
May 16–20, 1961	AMERICAN COLLEGE OF CARDIOLOGY, INC., New York, N. Y., Hotel Biltmore.
May 24, 1961	AMERICAN GASTROENTEROLOGICAL SOCIETY, Chicago, Ill., Drake Hotel.
June 22–23, 1961	AMERICAN RHEUMATISM ASSOCIATION, New York, N. Y., Coliseum.
June 22–26, 1961	AMERICAN COLLEGE OF CHEST PHYSICIANS, New York, N. Y., Hotel Commodore.

POSTGRADUATE COURSES

THE AMERICAN COLLEGE OF PHYSICIANS

SCHEDULE OF POSTGRADUATE COURSES, WINTER-SPRING, 1961

Jan. 9–13	Course No. 4, RECENT ADVANCES IN DRUG THERAPY: University of Washington School of Medicine, Seattle, Wash., Robert H. Williams, M.D., F.A.C.P., Director.
Jan. 16–20	Course No. 5, MECHANISMS OF DISEASE: Columbia University College of Physicians and Surgeons, Presbyterian Hospital, New York, N. Y.; Alfred P. Fishman, M.D., F.A.C.P., and Stanley E. Bradley, M.D., F.A.C.P., Co-Directors.

Feb. 20–24	Course No. 6, SELECTED TOPICS IN INTERNAL MEDICINE: The University of Oklahoma School of Medicine and University Hospitals, Oklahoma City, Okla.; Stewart G. Wolf, Jr., M.D., F.A.C.P., and James F. Hammarsten, M.D., F.A.C.P., Co-Directors; William O. Smith, M.D., (Associate), Associate Director.
Mar. 6–10	CARDIOVASCULAR DISEASES, Mount Sinai Hospital, Charles K. Friedberg, M.D., F.A.C.P., Director.
Mar. 13–17	INTERNAL MEDICINE, McGill University, Ronald V. Christie, M.D., F.A.C.P., Director.
Mar. 20–24	ADVANCED CLINICAL ELECTROCARDIOGRAPHY, The University of Tennessee, I. Frank Tullis, M.D., F.A.C.P., Director.
Mar. 23–25	ENDOCRINOLOGY, University of Virginia, William Parson, M.D., F.A.C.P., Director.
Apr. 12–15	PROBLEMS OF GROWTH AND AGING, Lankenau Medical Building, Philadelphia, Edward L. Bortz, M.D., F.A.C.P., Director.
May 15–19	GASTROENTEROLOGY, University of Pennsylvania School of Medicine; Henry L. Bockus, M.D., F.A.C.P., Director.
June 19–23	CURRENT ASPECTS OF INTERNAL MEDICINE, State University of Iowa, William B. Bean, M.D., F.A.C.P., Director.

OTHER POSTGRADUATE COURSE ANNOUNCEMENTS

Jan. 18, 19, 20

The Ninth Postgraduate Course in Diabetes and Basic Metabolic Problems of the American Diabetes Association will be held in New Orleans, Louisiana, on January 18, 19 and 20, 1961. The Course which is open to Doctors of Medicine is presented under the direction of the Committee on Professional Education of the American Diabetes Association. Chairman and Director, T. S. Danowski, M.D., Pittsburgh, Pa.; Vice Chairman, Arthur R. Colwell, Sr., M.D., Chicago, Illinois. All lectures will be held in the auditorium of the Louisiana State University School of Medicine.

First day of the course, Wednesday, January 18, on "Clinical Aspects of Lipids" is being held in coöperation with the Metabolism Study Section of the National Institutes of Health: Edward H. Ahrens, Jr., M.D., Chairman, and William H. Goldwater, Ph.D., Executive Secretary.

Fees: $40 for the three day Course for members of the American Diabetes Association; $75 for non-members. The full fee is payable at the time of filing application and includes the cost of the banquet to be held Wednesday evening, January 18. The fee will be returnable by the

Association to any registrant who submits his withdrawal in writing not later than January 6. *Fellows, residents, graduate students* and *interns,* in medicine and allied sciences in schools and hospitals in the *New Orleans area,* may attend the Scientific Sessions without charge, and should register by January 6. *Medical students* in the *New Orleans area* may register without charge after January 6, if space permits.

Accepted for 17 hours of credit, Category II, by American Academy of General Practice.

DALHOUSIE UNIVERSITY FACULTY OF MEDICINE, HALIFAX, N. S.

Jan. 30–31 and Feb. 1	PSYCHIATRY FOR THE PRACTITIONER. Professor R. O. Jones and Staff, Department of Psychiatry.
Feb. 27–Mar. 3	INFECTIONS AND INFECTIOUS DISEASES, Professor R. C. Dickson, Professor N. B. Coward and Staffs, Depts. of Medicine and Paediatrics.

HARVARD MEDICAL SCHOOL, BOSTON 15, MASS.

Feb. 1–Apr. 29	CARDIOLOGY: Louis Wolff, M.D., and Associates at the Beth Israel Hospital. Tuition: $500. For further information, write: Ass't. Dean, Courses for Graduates, Harvard Medical School, Boston 15, Mass.

YALE UNIVERSITY SCHOOL OF MEDICINE, 333 CEDAR ST., NEW HAVEN 11, CONN.

Feb. 1–Mar. 22 (Wednesdays, 7–9 P.M.)	DIAGNOSIS AND MANAGEMENT OF DISEASES OF THE KIDNEY. For further information contact: Arthur Ebbert, Jr., M.D., Associate Dean, Yale University School of Medicine, 333 Cedar Street New Haven 11, Conn.

TULANE UNIVERSITY SCHOOL OF MEDICINE, DIVISION OF GRADUATE MEDICINE, 1430 TULANE AVENUE, NEW ORLEANS 12, LA.

Feb. 8–11	ADOLESCENT MEDICINE. Dr. William D. Davis, Jr., Dr. Cyril Phillips, Dr. Keith Reemtsma, Dr. Charles P. Summerall, Dr. William G. Thurman, Dr. Norman Woody.
Mar. 2–4	RECENT ADVANCES IN DIAGNOSIS AND THERAPEUTIC TECHNIQUES IN CANCER. Dr. Robert Craft Smith, Chairman; Dr. Edward T. Krementz, Dr. Charles C. Sprague.
Apr. 13–15	NEWER CONCEPTS OF CARDIORESPIRATORY DISEASE IN CHILDREN. Dr. William Waring, Chairman; Dr. Oscar Creech, Dr. Marion Ledbetter.

QUEENS HOSPITAL CENTER, DEPT. OF HOSPITALS, JAMAICA, NEW YORK

Feb. 7	A four-months' course in the MEDICAL USES OF RADIOACTIVE ISOTOPES will be offered at the Queens Hospital Center by the Radiation Medicine Department. Course

will commence on Tuesday, February 7, 1961, and will consist of weekly five-hour sessions covering lectures, laboratory exercises, and clinical management of patients.

Enrollment will be limited. Tuition: $275. Apply to: Dr. Philip J. Kahan, Supervising Medical Superintendent, Queens Hospital Center, 82–68 164th Street, Jamaica 32, N. Y.

UNIVERSITY OF KANSAS MEDICAL CENTER, KANSAS CITY, KANSAS

Feb. 13–14 — HYPERTENSION. For further information write the Department of Postgraduate Medical Education, The University of Kansas School of Medicine, Kansas City 12, Kansas.

UNIVERSITY OF MINNESOTA, MINNEAPOLIS 14, MINN.

Feb. 13–18 — A continuation course in NEUROLOGY AND THE NEUROLOGIC ASPECTS OF INTERNAL DISEASE for general physicians and internists will be presented by the University of Minnesota from February 13 to 18, 1961, at the Center for Continuation Study.

Guest speakers will be Doctors Gilbert H. Glaser, Associate Professor and Chief, Section of Neurology, Yale University School of Medicine, New Haven, Connecticut; and James W. Stephens, Associate Professor, Department of Neurology, University of Colorado Medical School, Denver, Colorado.

The course will be presented under the direction of Dr. A. B. Baker, Professor and Director, Division of Neurology. The remainder of the faculty will include members of the faculties of the University of Minnesota Medical School and the Mayo Foundation.

Lodging and meal accommodations are available at the Center for Continuation Study.

For further information concerning the above course, write to the Director, Department of Continuation Medical Education, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14.

BOSTON CITY HOSPITAL, BOSTON, MASS.

Mar. 27–31 — THE MEASUREMENT OF PULMONARY FUNCTION IN HEALTH AND DISEASE: Boston City Hospital, Boston, Mass. Tuition: $100. ($75 for members of the American Thoracic Society.) Applications should be directed to: Edward J. Welch, M.D., F.A.C.P., Chairman of Course, 1101 Beacon Street, Brookline, Mass.

OTHER ANNOUNCEMENTS

The Third Annual Conference on Operable Heart Disease will take place at Presbyterian Medical Center in San Francisco on March 3 and 4, 1961. Those

interested may obtain further information by writing to the Conference Chairman, Dr. Frank Gerbode.

The Donner Laboratory, University of California, Berkeley, announces the availability of a fellowship in metabolism for the year 1961–62. The fellow may participate in various projects including isotopic studies in steroid metabolism, radiobiological research or other areas of investigation; and a minimum of courses in biophysics, medical physics, chemistry, mathematics or physics may be taken in the University. The followship will be awarded for one year with the possibility of renewal for one additional year. Applicants should have residency training in metabolism. For information write to the Director, Donner Laboratory, University of California, Berkeley 4, California; deadline for receipt of applications is February 7, 1961.

A research fellowship in clinical cardiovascular physiology is available in the Department of Medicine of the University of Southern California School of Medicine. The appointment is to be for a period of one to two years. Emphasis is on physiological investigation in patients and in animals for study of hemodynamic mechanisms of cardiovascular disease.

The American Association for the Study of Headache was organized during the summer of 1960 at the time of the Annual A. M. A. meeting in Miami. The following officers were elected: President, Henry D. Ogden, New Orleans, Louisiana; Vice-President, Walter C. Alvarez, Chicago, Illinois; Treasurer, Robert E. Ryan, St. Louis, Missouri; Secretary, Bayard T. Horton, Rochester, Minnesota; Moderator, George T. Waldbott, Detroit, Michigan.

The Association welcomes to its membership any physician—specialist or general practitioner—who is interested in the study of headache. Further information can be obtained from the Secretary, Doctor Bayard Horton, Mayo Clinic, Rochester, Minnesota.

MAURICE C. PINCOFFS, M.D.

As this issue of the ANNALS goes to press, we learn with sorrow of the death of Dr. Maurice C. Pincoffs on December 8, 1960, in Baltimore. For 27 years as Editor, Dr. Pincoffs *was* the ANNALS. We know that all readers of the journal will share our grief over his untimely passing, and will feel a debt of gratitude for the great service rendered by him in his editorial capacity.

IN EMOTIONALLY PROJECTED SMOOTH-MUSCLE SPASM...

Prompt, Profound Protection...at both ends of the vagus

PRO-BANTHĪNE® *with* DARTAL®

Professional reliance on the therapeutic proficiency of Pro-Banthīne in functional gastrointestinal disorders has made it the most widely prescribed anticholinergic.

The consistent relief of emotional tensions afforded by Dartal makes this well-tolerated tranquilizer a rational choice to support the antispasmodic action of Pro-Banthīne in emotionally influenced smooth-muscle spasm.

These two reliable agents combined as Pro-Banthīne with Dartal consistently control both disturbed mood and disordered motility when emotional disturbances project themselves through the vagus to provoke such gastrointestinal dysfunctions as gastritis, pylorospasm, peptic ulcer, spastic colon or biliary dyskinesia.

USUAL ADULT DOSAGE:
One tablet three times a day.

SUPPLIED as aqua-colored, compression-coated tablets containing 15 mg. of Pro-Banthīne (brand of propantheline bromide) and 5 mg. of Dartal (brand of thiopropazate dihydrochloride).

G. D. SEARLE & CO.
Chicago 80, Illinois
Research in the Service of Medicine

"Gratifying" relief from

for your patients with
'low back syndrome' and
other musculoskeletal disorders

POTENT muscle relaxation
EFFECTIVE pain relief
SAFE for prolonged use

stiffness and pain

"gratifying" *relief from stiffness and pain in 106-patient controlled study*

(as reported in J.A.M.A., April 30, 1960)

"Particularly gratifying was the drug's [SOMA's] ability to relax muscular spasm, relieve pain, and restore normal movement . . . Its prompt action, ability to provide objective and subjective assistance, and freedom from undesirable effects recommend it for use as a muscle relaxant and analgesic drug of great benefit in the conservative management of the 'low back syndrome'."

Kestler, O.: Conservative Management of "Low Back Syndrome", J.A.M.A. 172: 2039 (April 30) 1960.

FASTER IMPROVEMENT—79% complete or marked improvement in 7 days (Kestler).

EASY TO USE—Usual adult dose is one 350 mg. tablet three times daily and at bedtime.

SUPPLIED: 350 mg., white tablets, bottles of 50.
For pediatric use, 250 mg., orange capsules, bottles of 50.

Literature and samples on request.

SOMA®
(CARISOPRODOL WALLACE)

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an antibiotic capsule with an added measure of protection

AGAINST RELAPSE – up to 6 days' activity with 4 days' dosage

AGAINST "PROBLEM" PATHOGENS – uniformly sustained peak activity

AGAINST SECONDARY INFECTION – full antibiotic response

DISTINCTIVE, DRY-FILLED, DUOTONE RED CAPSULES – 150 mg., bottles of 16 and 100. Dosage: 1 capsule (150 mg.) four times daily. Precautions: As with other antibiotics, DECLOMYCIN may occasionally give rise to glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis or dermatitis. A photodynamic reaction to sunlight has been observed in a few patients on DECLOMYCIN. Although reversible by discontinuing therapy, patients should avoid exposure to intense sunlight. If adverse reaction or idiosyncrasy occurs, discontinue medication. Overgrowth of nonsusceptible organisms is a possibility with DECLOMYCIN, as with other antibiotics. The patient should be kept under constant observation.

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DEMETHYLCHLORTETRACYCLINE LEDERLE

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in arthritis and allied disorders

Butazolidin

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Proved by a Decade of Experience
Confirmed by 1700 Published Reports
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Since its anti-inflammatory properties were first noted in Geigy laboratories 10 years ago, time and experience have steadily fortified the position of Butazolidin as a leading nonhormonal anti-arthritic agent. Indicated in both chronic and acute forms of arthritis, Butazolidin is noted for its striking effectiveness in relieving pain, increasing mobility and halting

Butazolidin®, brand of phenylbutazone: Red, sugar-coated tablets of 100 mg. Butazolidin® Alka: Orange and white capsules containing Butazolidin 100 mg.; dried aluminum hydroxide gel 100 mg.; magnesium trisilicate 150 mg.; hexatropine methylbromide 1.25 mg.

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CAPSULES

BRINGS DOWN
HOLDS DOWN high cholesterol levels–today's

Each LUFA capsule provides:

Unsaturated Fatty Acids**	378 mg
Pyridoxine HCl (B_6)	2 mg
Choline Bitartrate	233 mg
dl, Methionine	110 mg
Inositol	40 mg
Desiccated Liver	87 mg
Vitamin B_{12}	1 mc
Vitamin E (dl,alpha-tocopheryl acetate)	3.5 I.U

**from specially refined safflower seed o
Provides approximately 294 mg. of linoleic aci

every patient with

hypercholesterolemia

obesity

diabetes

angina pectoris

post-coronary infarction

deserves the benefit potentials of Lufa

SAFE • SIMPLE • ECONOMICAL

1. LUFA's unsaturated fatty acids offset the atherogenic effects of dietary saturated (animal) fatty acids.*

2. LUFA helps improve metabolism of cholesterol, lipoproteins and other lipids by promoting normal liver function.

major concept in control of Atherosclerosis

dosage: Therapeutic, 6 to 9 capsules daily, in divided doses. Maintenance, one capsule b.i.d. or t.i.d.

supplied: Bottles of 100, 500 and 1000 capsules.

*Special anti-atherogenic diet sheets for patient distribution and LUFA samples and literature on request.

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250 East 43rd Street, New York 17, N. Y.

above: normal arterial lumen
below: extensive narrowing due to cholesterol

patient with congestive heart failure; ascites and 4+ edema to the knee

with Esidrix, 12½ pounds lost in 13 days; basilar râles and ascites no longer present; pitting edema cleared

Photos used with permission of the patient.

benefits in edema, benefits in hypertension plus built-in potassium protection

NEW ESIDRIX-K®

New ESIDRIX-K provides all the oral diuretic-antihypertensive advantages of ESIDRIX, plus a generous potassium supplement. ESIDRIX produces marked excretion of salt and water in edematous patients, and in many hypertensive patients significantly reduces blood pressure, alone or with other antihypertensive drugs. Potassium excretion is minimal, and the built-in K supplement further helps eliminate problems due to potassium loss. Three ESIDRIX-K tablets provide potassium equivalent to one quart of fresh orange juice; ESIDRIX-K is coated to prevent gastric irritation.

Complete information sent on request.

Supplied: Esidrix-K Tablets (white, coated), each containing 25 mg. Esidrix and 500 mg. potassium chloride. Esidrix Tablets, 25 mg. (pink, scored) and 50 mg. (yellow, scored).

Esidrix-K is especially indicated for patients in whom even moderate potassium loss can cause complications, or those whose condition predisposes to hypokalemia. Among candidates for Esidrix-K are patients taking digitalis for congestive heart failure, those with renal or liver disease, those under long-term treatment, and those on salt-restricted diets.

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SUMMIT, NEW JERSEY

ESIDRIX® (hydrochlorothiazide CIBA)

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a pair of cardiac patients:

both are free of pain—but only one is on

DILAUDID®

(Dihydromorphinone HCl)

swift, sure analgesia normally unmarred by nausea and vomiting

DILAUDID provides unexcelled analgesia in acute cardiovascular conditions. Onset of relief from pain is almost immediate. The high therapeutic ratio of DILAUDID is commonly reflected by lack of nausea and vomiting—and marked freedom from other side-effects such as dizziness and somnolence.

by mouth **by needle** **by rectum**

2 mg., 3 mg., and 4 mg.

May be habit forming—usual precautions should be observed as with other opiate analgesics.

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ROMILAR has one specific central action: raising the cough reflex threshold.[1] There is no analgesic effect, no central depression.[1-7] Cough control begins within 15 to 30 minutes and lasts for as long as six hours.[7] ROMILAR is a unique cough specific: it provides the antitussive potency of codeine with the safety of a placebo.[3] There is no tolerance liability, no addictive potential.[1,3-8]

ROMILAR is of special value when cough suppression is vital—in patients with pulmonary and cardiac disease, hernia or rib fracture, before and after abdominal and EENT surgery and during i.v. infusions.

SUPPLY: Syrup in bottles of 4 oz, 16 oz, 1 gal. Tablets in bottles of 20, 100, 500. Expectorant in bottles of 16 oz, 1 gal.

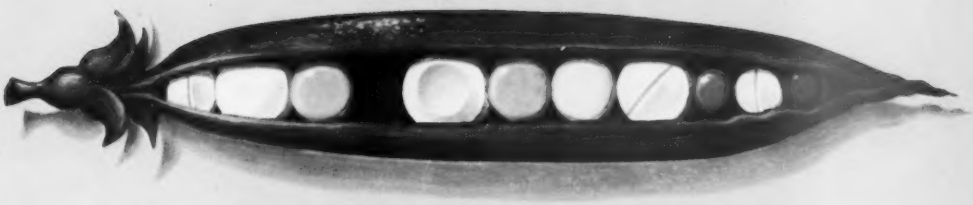
REFERENCES: 1. H. A. Bickerman in W. Modell, Ed., Drugs of Choice 1958-1959, St. Louis, The C. V. Mosby Company, p. 557. 2. L. J. Cass and W. S. Frederik, New England J. Med., 249:132, 1953. 3. L. J. Cass, W. S. Frederik and J. B. Andosca, Am. J. M. Sc., 227:291, 1954. 4. H. Isbell and H. F. Fraser, J. Pharmacol. & Exper. Therap., 107:524, 1953. 5. W. M. Benson, P. L. Stefko and L. O. Randall, J. Pharmacol. & Exper. Therap., 109:189, 1953. 6. New and Nonofficial Drugs 1959, Philadelphia, J. B. Lippincott Company, 1959, p. 326. 7. N. Ralph, Am. J. M. Sc., 227:297, 1954. 8. H. A. Bickerman, E. German, B. M. Cohen and S. E. Itkin, Am. J. M. Sc., 234:191, 1957.

Romilar®
Hydrobromide—brand of dextromethorphan hydrobromide

NON-NARCOTIC COUGH SPECIFIC WITH PROMPT, PROLONGED ACTION

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, N. J.

the cough control is specific



how does **Mellaril** *differ from other potent tranquilizers?*

Mellaril®

THIORIDAZINE HCl

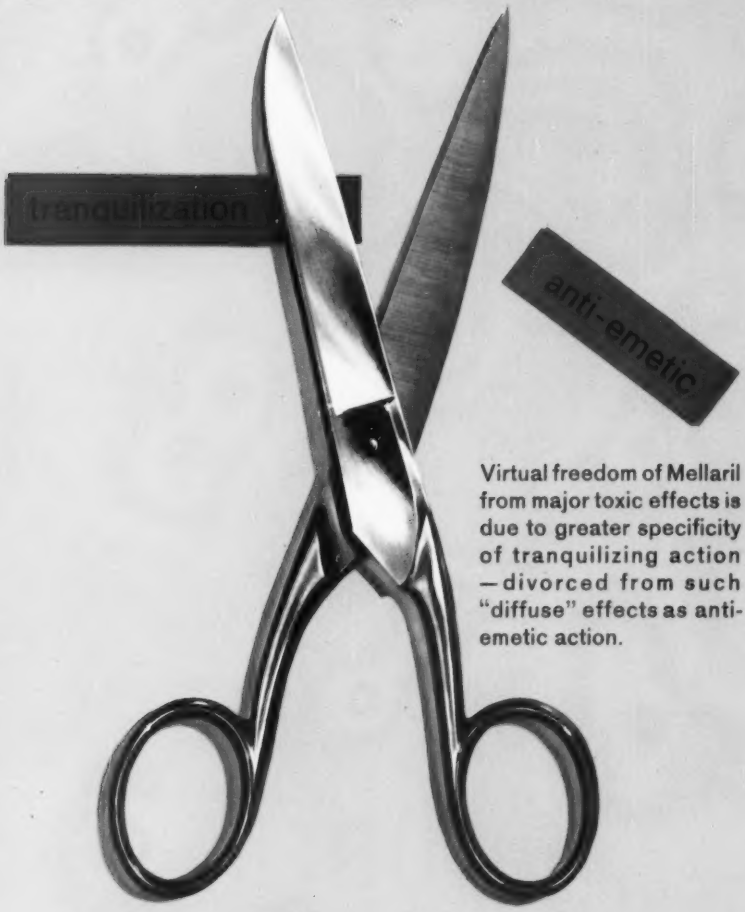
provides highly effective tranquilization,
relieves anxiety, tension, nervousness,

but is virtually free of such toxic effects as

jaundice
Parkinsonism
blood dyscrasia
dermatitis

SANDOZ

greater specificity of tranquilizing action results in fewer side effects



Virtual freedom of Mellaril from major toxic effects is due to greater specificity of tranquilizing action—divorced from such "diffuse" effects as anti-emetic action.

Mellaril

THIORIDAZINE HCl

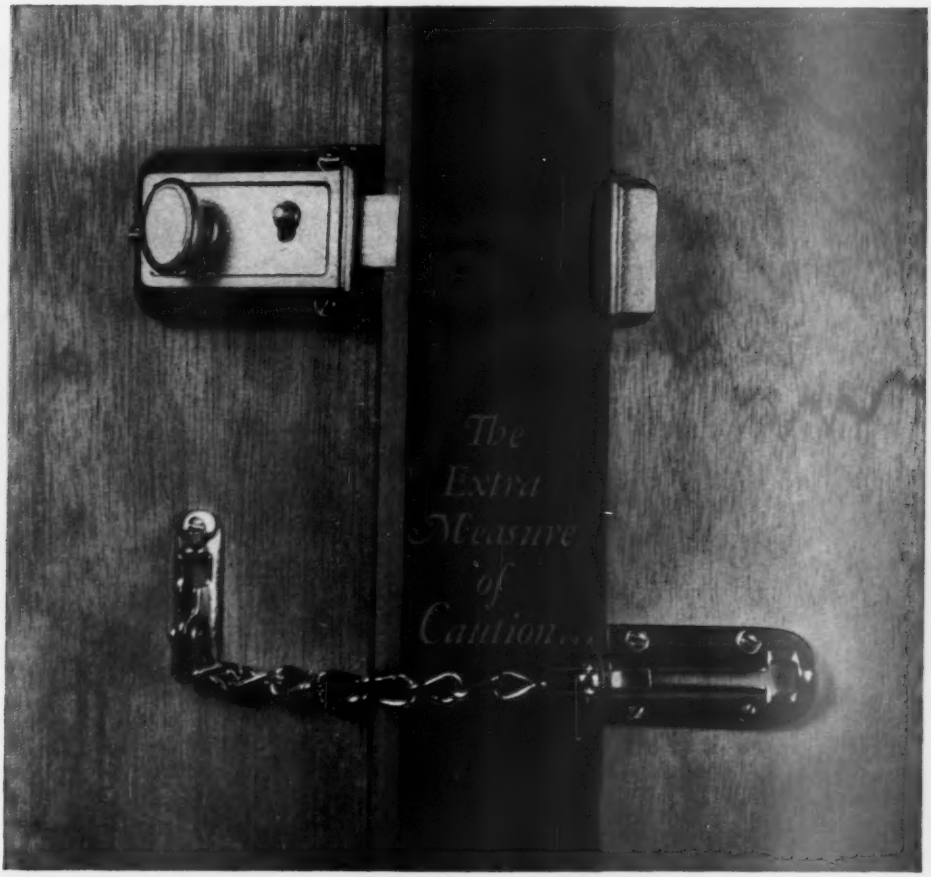
specific, effective tranquilizer

"A new phenothiazine derivative, thioridazine [Mellaril®], was used to treat 71 patients, most of whom were unduly agitated and disturbed due to hospitalization for medical or surgical conditions....The response to treatment was considered satisfactory in 83.4 per cent of patients....In agreement with the published results of other investigators, we believe that thioridazine shows a greater specificity of tranquilizing action and freedom from serious toxic effects when compared with some of the other phenothiazines."*

Supply: MELLARIL Tablets, 10 mg., 25 mg., 50 mg., 100 mg.

SANDOZ

*David, N. A.; Logan, N. D., and Porter, G. A.: Evaluation of Thioridazine (Mellaril), a New Phenothiazine, in The Hospitalized Patient. A.M. & C.T. 7:364 (June) 1960.



Tetracycline now combined with the new, more active antifungal antibiotic – Fungizone – for broad spectrum therapy / antimonilial prophylaxis

A new advance in broad spectrum antibiotic therapy, MYSTECLIN-F provides all the well-known benefits of tetracycline and also contains the new, clinically proved antifungal antibiotic, Fungizone. This Squibb-developed antibiotic, which is unusually free of side effects on oral administration when given in oral prophylactic doses, has substantially greater in vitro activity than nystatin against strains of Candida (Monilia) albicans.

Thus, in addition to providing highly effective broad spectrum therapy, MYSTECLIN-F prevents the monilial overgrowth in the gastrointestinal tract so commonly associated with such therapy. It helps to protect the patient from troublesome, even serious, monilial complications.

New Mysteclin-F provides this added antifungal protection at little increased cost to your patients over ordinary tetracycline preparations.

Available as: MYSTECLIN-F CAPSULES (250 mg./50 mg.) MYSTECLIN-F HALF STRENGTH CAPSULES (125 mg./25 mg.) MYSTECLIN-F FOR SYRUP (125 mg./25 mg. per 5 cc.) MYSTECLIN-F FOR AQUEOUS DROPS (100 mg./20 mg. per cc.)

For complete information, consult package insert or write to Professional Service Department, Squibb, 745 Fifth Avenue, N. Y. 22, N. Y.

NEW

MYSTECLIN-F

Squibb Phosphate-Potentiated Tetracycline (SUMYCIN) *plus* Amphotericin B (FUNGIZONE)

SQUIBB *Squibb Quality – the Priceless Ingredient*

"MYSTECLIN", "SUMYCIN" AND "FUNGIZONE" ARE SQUIBB TRADEMARKS

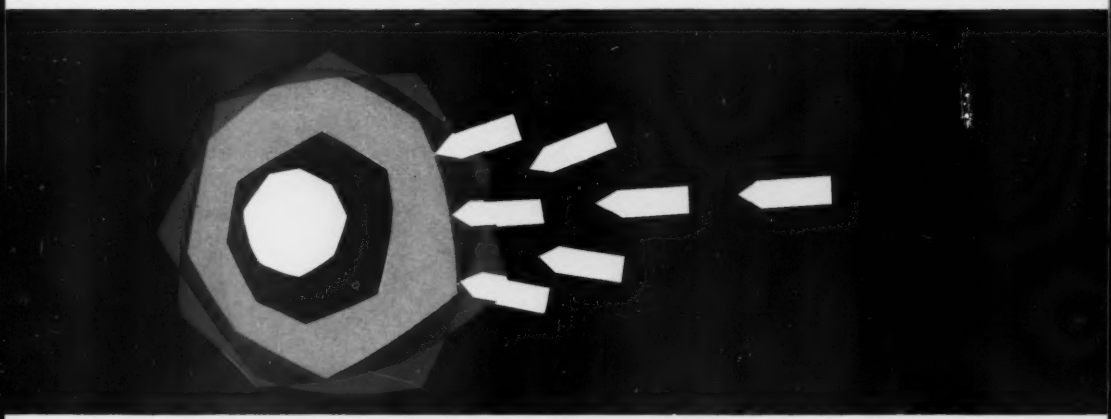
In The Hospitalized Patient. A.M. & C.T. 7:364 (June) 1960.

to meet the allergic attack...with b.i.d. dosage

tacaryl T.M.

METHDILAZINE HYDROCHLORIDE, MEAD JOHNSON

inherently sustained action at the cellular level



inherently sustained action

Tacaryl possesses inherent long-acting properties. After rapid disappearance from the blood stream, Tacaryl is bound to the tissues. This protective affinity for tissue provides a notably sustained effect which does not depend upon the use of artificial, long-acting construction. The sustained action, an inherent property of the molecule, lasts for periods up to 12 hours.

rapid absorption–rapid relief

Tacaryl is absorbed quickly to provide relief of symptoms within an hour.

low toxicity–minimal side effects

In studies to date,[1] side effects were minimal; in a small percentage of patients, mild drowsiness was observed. Tolerance was not reported even after long usage. No cumulative effect has been observed.

clinically proved

In studies of 459 patients,[1] Tacaryl provided effective symptomatic relief in a wide variety of conditions, including allergic rhinitis, pruritus, various skin disorders, allergic bronchial asthma, pruritus of chickenpox, and allergic conjunctivitis. In some cases, the relief of itching bordered on the dramatic.[2] In a double-blind clinical evaluation[3] of various antihistaminic agents in hay fever, Tacaryl provided benefits in all patients with moderate to severe symptoms.

dosage: *adults*—One tablet (8 mg.) or two 5 cc. teaspoonfuls syrup (8 mg.) twice daily. *children*—One-half tablet (4 mg.) or one 5 cc. teaspoonful syrup (4 mg.) twice daily.

In some cases it may be desirable to adjust dosage to meet individual requirements.

supply: Scored tablets, 8 mg., bottles of 100. Syrup, 4 mg. per 5 cc. teaspoonful, 16 oz. bottles.

references: (1) Clinical Research Division, Mead Johnson & Company. (2) Howell, C. M., Jr.: Evaluation of Methdilazine Hydrochloride as an Antipruritic Agent, North Carolina M. J. *21* (May) 1960 (in press). (3) Wahner, H. W., and Peters, C. A.: An Evaluation of Some Newer Antihistaminic Drugs Against Pollinosis, Proc. Staff Meet. Mayo Clin. *35*:161-169 (March 30) 1960.

Mead Johnson
Symbol of service in medicine

17760

Helps you take the misery out of menopause

as hormones alone often don't do

Fast-acting Milprem directly relieves both emotional dread and estrogen deficiency

Dosage: One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

Composition: Miltown (meprobamate) + conjugated estrogens (equine).

Supplied: **Milprem-400**, each coated pink tablet contains 400 mg. Miltown and 0.4 mg. conjugated estrogens (equine). **Milprem-200**, each coated old-rose tablet contains 200 mg. Miltown and 0.4 mg. conjugated estrogens (equine). Both potencies in bottles of 60.

Literature and samples on request.

Many physicians find that estrogen therapy is not enough for the woman who is also filled with anxiety by her menopause. Her emotional dread may make her so miserable that it becomes a real clinical problem.

This is where Milprem helps you so much. It calms the woman's anxiety and tension; prevents moody ups and downs; relieves her insomnia and headache. At the same time, it checks hot flushes by replacing lost estrogens. The patient feels better than she did on estrogen therapy alone. And your counsel and your assurances can now help her make her adjustment much faster.

Milprem®

(Miltown® plus natural estrogens)

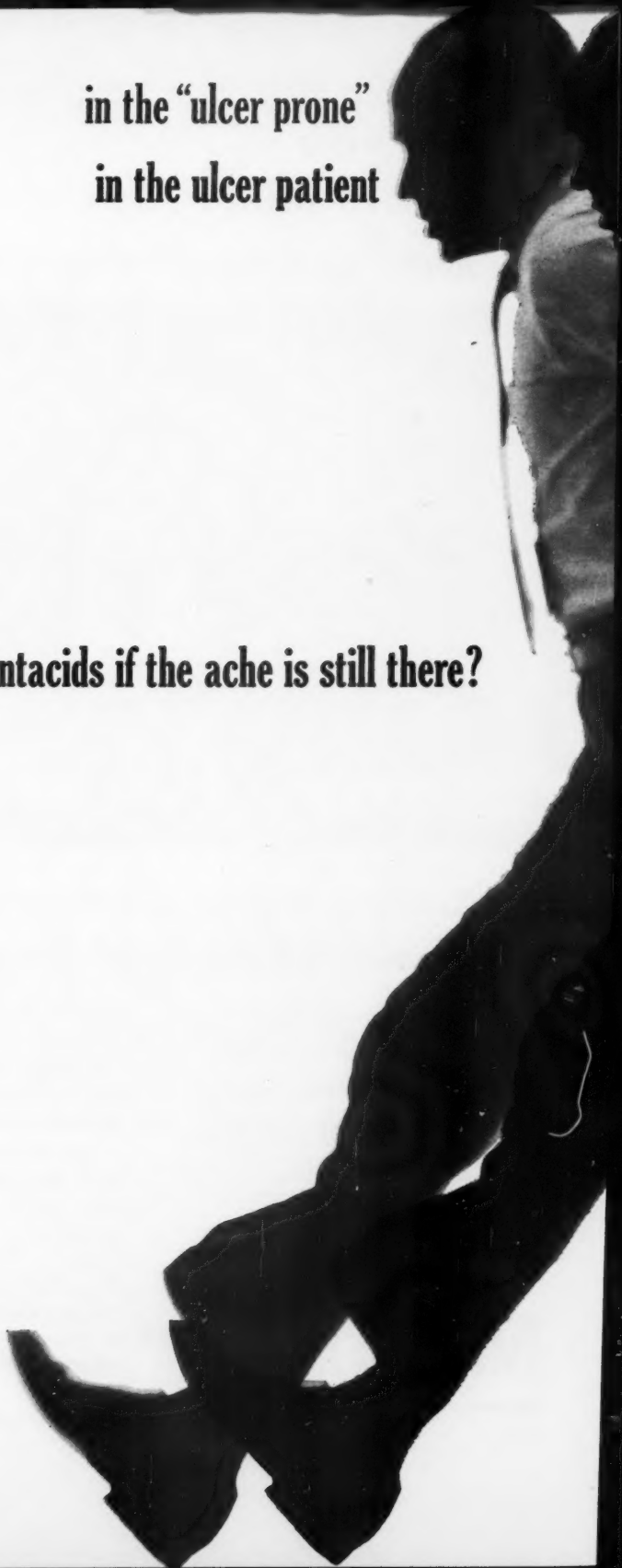
CMP-1306

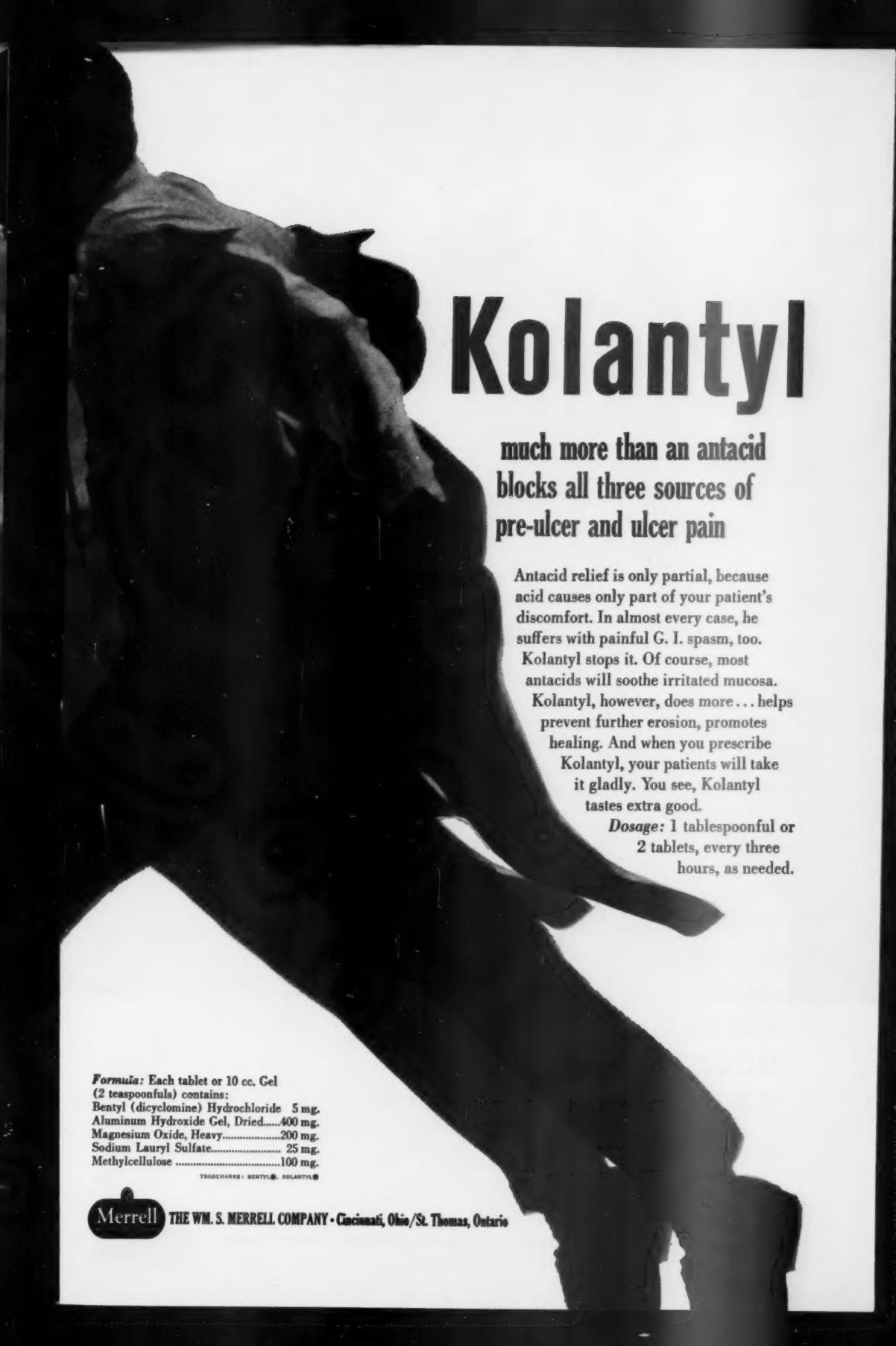
WALLACE LABORATORIES / *Cranbury, N. J.*

in the "ulcer prone"

in the ulcer patient

...what good are antacids if the ache is still there?





Kolantyl

much more than an antacid blocks all three sources of pre-ulcer and ulcer pain

Antacid relief is only partial, because acid causes only part of your patient's discomfort. In almost every case, he suffers with painful G. I. spasm, too. Kolantyl stops it. Of course, most antacids will soothe irritated mucosa. Kolantyl, however, does more . . . helps prevent further erosion, promotes healing. And when you prescribe Kolantyl, your patients will take it gladly. You see, Kolantyl tastes extra good.

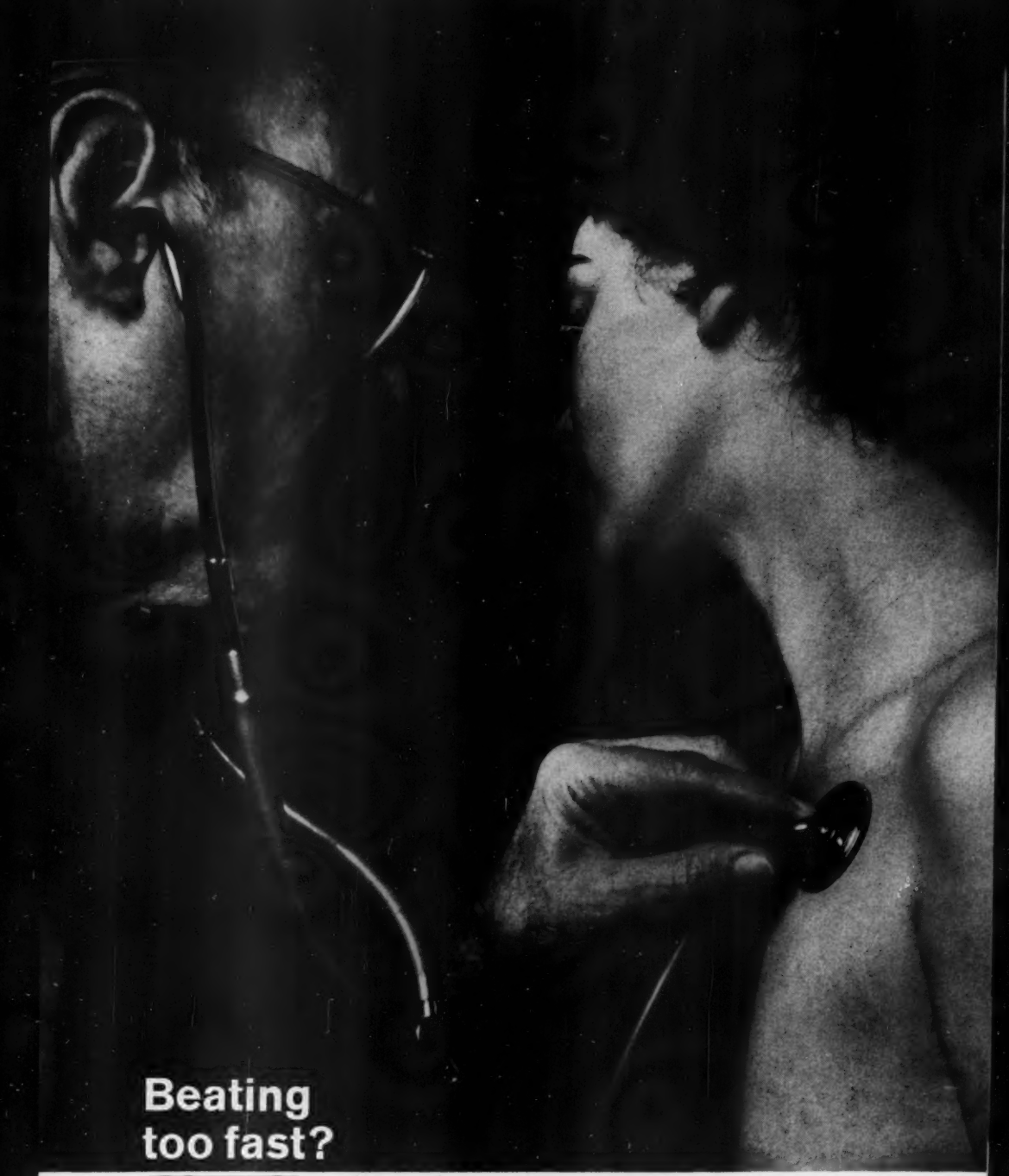
Dosage: 1 tablespoonful or 2 tablets, every three hours, as needed.

Formula: Each tablet or 10 cc. Gel (2 teaspoonfuls) contains:

Bentyl (dicyclomine) Hydrochloride	5 mg.
Aluminum Hydroxide Gel, Dried	400 mg.
Magnesium Oxide, Heavy	200 mg.
Sodium Lauryl Sulfate	25 mg.
Methylcellulose	100 mg.

TRADEMARKS: BENTYL®, KOLANTYL®

Merrell THE WM. S. MERRELL COMPANY • Cincinnati, Ohio/St. Thomas, Ontario



Beating too fast?

Slow it down with SERPASIL®

(reserpine CIBA)

Serpasil has proved effective as a heart-slowing agent in the following conditions: mitral disease; myocardial infarction; cardiac arrhythmias; neurocirculatory asthenia; thyroid toxicosis; excitement and effort syndromes; cardiac neurosis; congestive failure. Serpasil should be used with caution in patients receiving digitalis and quinidine. It is not indicated in cases of aortic insufficiency.

SUPPLIED: Tablets, 0.1 mg., 0.25 mg. (scored) and 1 mg. (scored). Complete information available on request.

CIBA

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FOR PROVEN MENOPAUSAL BENEFITS with extra relief from anxiety and tension

The vast majority of menopausal women, *especially on the first visit,* are nervous, apprehensive, and tense. PMB-200 or PMB-400 gives your patient the advantage of *extra* relief from anxiety and tension, particularly when the patient is "high strung," under prolonged emotional stress, or when psychogenic manifestations are acute.

Proven menopausal benefits are confirmed by the wide clinical acceptance of "Premarin," specifically for the relief of hot flushes and other symptoms of estrogen deficiency, together with the well established tranquilizing efficacy of meprobamate.

Two potencies to meet the needs of your patients:

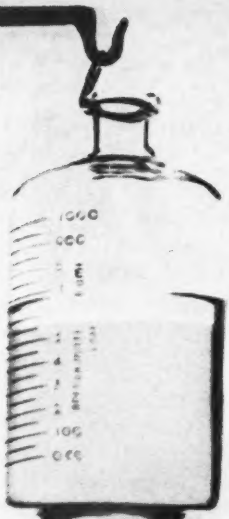
PMB 200

"PREMARIN"® WITH MEPROBAMATE*

PMB-200—Each tablet contains conjugated estrogens equine ("Premarin") 0.4 mg., and 200 mg. of meprobamate. When greater tranquilization is necessary you can prescribe PMB-400 – Each tablet contains conjugated estrogens equine ("Premarin") 0.4 mg., and 400 mg. of meprobamate. Both potencies are available in bottles of 60 and 500.

AYERST LABORATORIES
New York 16, N.Y., Montreal, Canada

*MEPROBAMATE, LICENSED UNDER U. S. PAT. NO. 2,724,720. 6012



Introducing
a completely new
water-soluble salt
of FURADANTIN

NEW FURADANTIN® SODIUM

brand of nitrofurantoin

for Intravenous Use
where oral medication is not feasible

for treating
genitourinary infections, such as
pyelonephritis, pyelitis, cystitis, prostatitis
systemic, bacterial infections
has been lifesaving in certain instances

(COPY OF PACKAGE INSERT)

FURADANTIN®

brand of nitrofurantoin

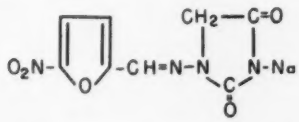
SODIUM

STERILE

For Intravenous Use

ACTIVE INGREDIENT: Each vial contains sufficient material to permit withdrawal of 180 mg. Furadantin, as the sodium salt.

Furadantin Sodium is a synthetic antibacterial agent, one of the antimicrobial nitrofurans, having the following structure:



1-(5-nitrofurfurylideneamino)-hydantoin sodium

INDICATIONS: The antibacterial spectrum of Furadantin encompasses gram-negative organisms such as E. coli, K. pneumoniae and certain strains of Proteus sp., Pseudomonas sp., and Aerobacter sp.; as well as gram-positive organisms such as staphylococci, streptococci, pneumococci, Clostridium sp., B. subtilis.

Furadantin Sodium is indicated in genitourinary infections such as pyelonephritis, pyelitis, cystitis and prostatitis, when the oral form is not feasible. It is also indicated in systemic bacterial infections with the exception of septicemias (bacteremias) unless other therapy has failed or until further work has demonstrated its activity in this condition caused by organisms sensitive in vitro to Furadantin.

In genitourinary tract infections, peroral therapy should replace intravenous when possible. It is not intended to replace surgery when mechanical obstruction or stasis is present.

ADMINISTRATION AND DOSAGE: The crystals must be dissolved just prior to use as follows: Add 15 cc. of 5% Dextrose Injection, USP, or Water for Injection, USP, to the vial of dry sterile Furadantin Sodium. Empty the syringe forcefully. Shake well to insure complete solution.

FURTHER DILUTION IS REQUIRED
BASED UPON THE PATIENT'S WEIGHT:

Patients weighing over 120 pounds. The recommended dose is 180 mg. of Furadantin in 500 cc. of diluent, twice daily. This is prepared as follows: Withdraw the solution of 180 mg. of Furadantin from the vial and add it to 500 cc. of 5% Dextrose in water, 5% Dextrose in Saline, Normal Saline or 1/6 molar Sodium Lactate intravenous solution. This final solution is to be given by intravenous drip at the usual rate.

Patients weighing under 120 pounds. The recommended dose is 3 mg./lb. of body weight per day divided in two equal doses. This is calculated on the basis that when the Furadantin Sodium in each vial is dissolved in 15 cc. of diluent, each cc. of solution represents 12 mg. of Furadantin. To prepare the final solution, each cc. of the initial Furadantin dilution should be added to a minimum of 33 cc. of parenteral fluid.

CAUTION: In the presence of impairment of renal function or acidosis administer Furadantin Sodium intravenously with caution as with any potent antibacterial agent. If employed under such circumstances the blood pH, CO_2 content or combining power and urea nitrogen or non-protein nitrogen should be followed closely.

The occurrence of a few cases of hemolytic anemia during Furadantin therapy has appeared in the literature.* A small percentage of negroes and ethnic groups of Mediterranean and Near-Eastern origin has an intrinsic abnormality of the red blood cells. As a result, hemolysis may occur with fava beans and certain drugs, such as primaquine. Thus it is advisable to closely observe such patients receiving Furadantin and to discontinue its administration if there is any indication of this condition developing.

SIDE REACTIONS: If nausea or emesis occur, these may be minimized by slowing the rate of administration, or by decreasing the dosage.

Sensitization occurs rarely in the form of an erythematous, maculopapular cutaneous eruption or urticaria. This is readily controlled by discontinuing treatment.

Occasionally a patient may show minor side reactions such as headache or malaise. No stomatitis, colitis, proctitis, anal pruritus or hematopoietic, renal or hepatic toxicity, have been reported with Furadantin Sodium.

PACKAGING: Sterile 20 cc. vials, containing one adult dose of crystalline sterile Furadantin Sodium (equivalent to 180 mg. of Furadantin).

CAUTION: Federal Law prohibits dispensing without prescription.

NOTE: DO NOT ADMINISTER INTRAMUSCULARLY. DO NOT USE WITHOUT DILUTING. MIX JUST PRIOR TO USE.

*West, M. and Zimmerman, H. H.: Hemolytic Anemia in Patient Receiving Nitrofurantoin (Furadantin), J.A.M.A. 162:637 (Oct. 13) 1956. Kimbro, E. L., Jr.: Sachs, M. F.; and Torbert, J. V. Jr.: Mechanism of Hemolytic Anemia Induced by Nitrofurantoin (Furadantin), Fed. Proc. 16:312 (Mar.) 1957.

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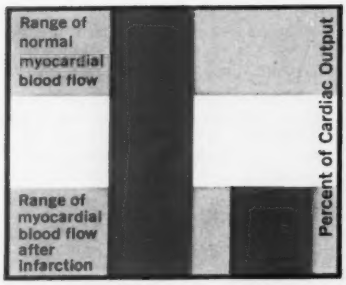
confirmed by radioisotopic measurements
in coronary artery disease

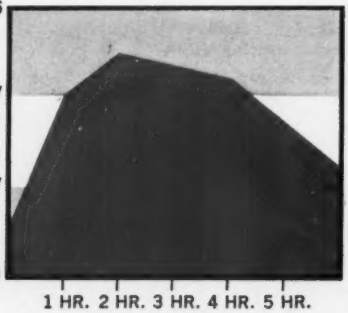
*Peritrate produces "significant" and "prolonged" increase in myocardial blood flow**

MYOCARDIAL BLOOD FLOW IN NORMAL AND POSTCORONARY PATIENTS



There is a significant reduction in myocardial blood flow in patients with a previous myocardial infarction.

EFFECTS OF PERITRATE ON POSTCORONARY PATIENTS



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Peritrate helps establish and sustain collateral circulation safely, supports natural healing and minimizes ensuing anginal attacks.

*Johnson, P. C., and Sevelius, G.:
Measurement of myocardial blood flow, J.A.M.A. *173*:1231 (July 16) 1960.

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brand of pentaerythritol tetranitrate

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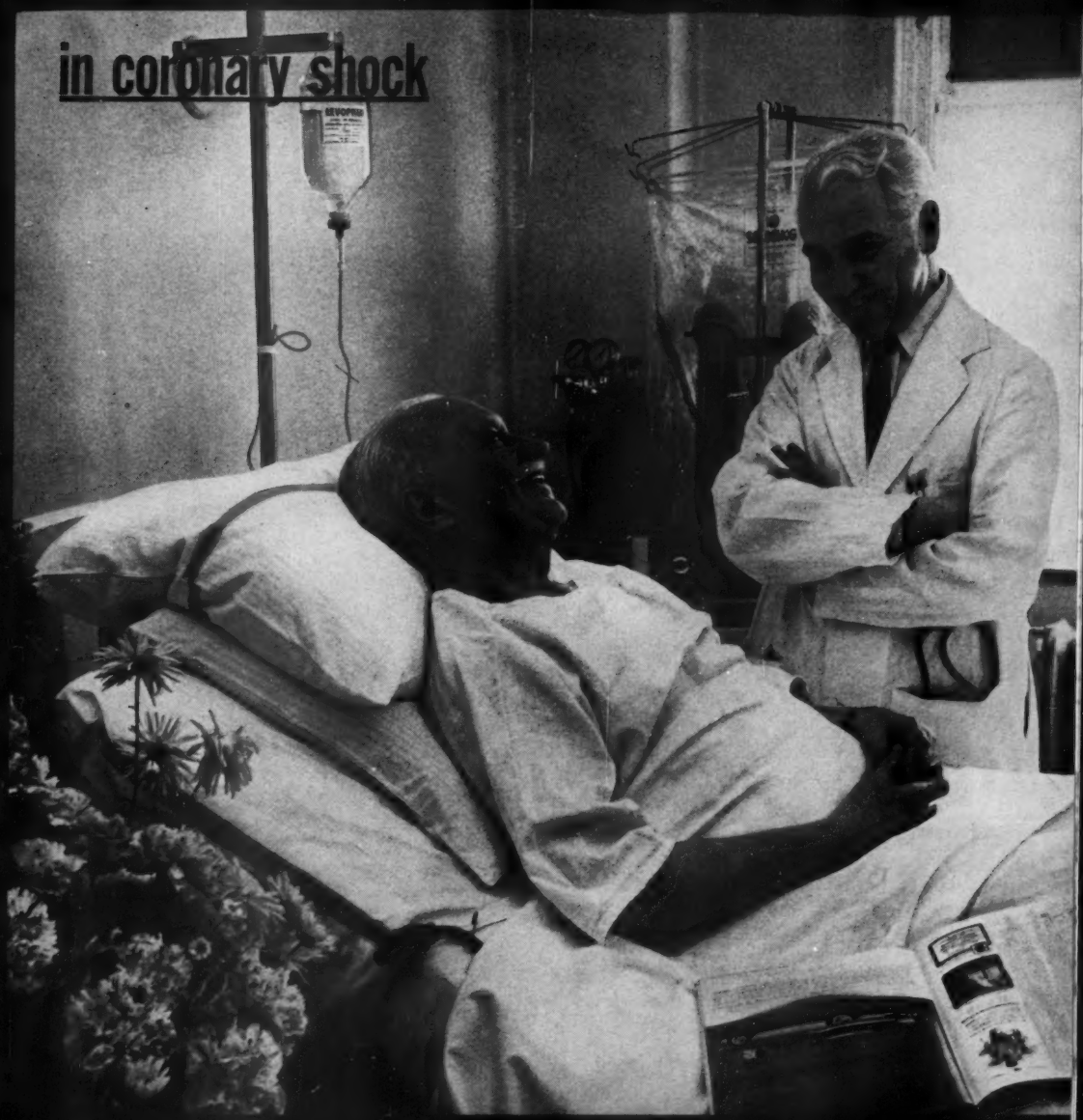

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1. Miller, A. J., and Moser, E. A.: J.A.M.A. 169:2000, April 25, 1959.

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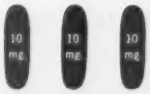
The daily 

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1. Biegeleisen, H. I.: Clin. Med. 2:1005, 1955. 2. Roberts, J. T.: Clin. Med. 4:1375, 1957. © 1960, A.P. Co.

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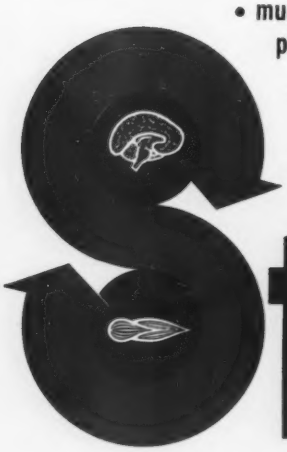

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Bibliography *(13 clinical studies, 858 patients)*: **1.** Alexander, L. (35 patients): Chemotherapy of depression — Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. **2.** Bateman, J. C. and Carlton, H. N. (50 patients): Meprobamate and benactyzine hydrochloride (Deprol) as adjunctive therapy for patients with advanced cancer. Antibiotic Med. & Clin. Therapy 6:648, Nov. 1959. **3.** Beerman, H. M. (44 patients): The treatment of depression with meprobamate and benactyzine hydrochloride. Western Med. 1:10, March 1960. **4.** Bell, J. L., Tauber, H., Santy, A. and Pulito, F. (77 patients): Treatment of depressive states in office practice. Dis. Nerv. System 20:263, June 1959. **5.** Breitner, C. (31 patients): On mental depressions. Dis. Nerv. System 20:142, (Section Two), May 1959. **6.** Gordon, P. E. (50 patients): Deprol in the treatment of depression. Dis. Nerv. System 21:215, April 1960. **7.** Landman, M. E. (50 patients): Clinical trial of a new antidepressive agent. J. M. Soc. New Jersey. In press, 1960. **8.** McClure, C. W., Papas, P. N., Speare, G. S., Palmer, E., Slattery, J. J., Konefal, S. H., Henken, B. S., Wood, C. A. and Ceresia, G. B. (128 patients): Treatment of depression — New technics and therapy. Am. Pract. & Digest Treat. 10:1525, Sept. 1959. **9.** Pennington, V. M. (135 patients): Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. 7:656, Aug. 1959. **10.** Rickels, K. and Ewing, J. H. (35 patients): Deprol in depressive conditions. Dis. Nerv. System 20:364, (Section One), Aug. 1959. **11.** Ruchwarger, A. (87 patients): Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia 28:438, Aug. 1959. **12.** Settel, E. (52 patients): Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination. Antibiotic Med. & Clin. Therapy 7:28, Jan. 1960. **13.** Splitter, S. R. (84 patients): Treatment of the anxious patient in general practice. J. Clin. & Exper. Psychopath. In press, April-June 1960.

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1. Cameron, E.: The Use of Tofranil in the Aged, Canad. Psychiat. A. J. Special Supplement, **4**:S160, 1959. 2. Christe, P.: Indications for Tofranil in Geriatrics, Schweiz. med. Wchnschr. **90**:586, 1960. 3. Schmied, J., and Ziegler, A.: Tofranil in Geriatrics, Praxis **49**:472, 1960.

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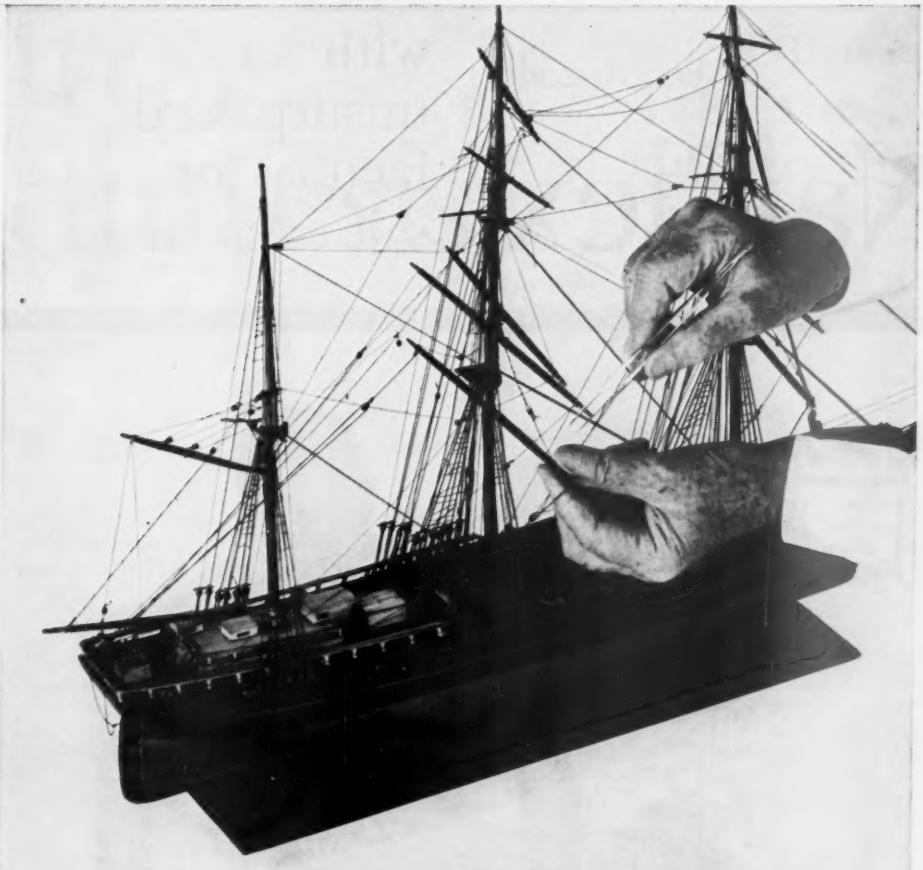

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1. Schwab, R. S. and England, A. C.: *J. Chron. Dis. 8*:488 (Oct.) 1958.
2. Schwab, R. S.: *Geriatrics 14*:545 (Sept.) 1959.
3. Doshay, L. J. *et al.*: *J.A.M.A. 160*:348 (Feb. 4) 1956.

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Supply: Available in yellow, scored 50 mg. tablets.

References: 1. Ford, R. V., Cur. Therap. Res., 2:51, 1960. 2. Pitts, R. F., Am. J. Med., 24:745, 1958.

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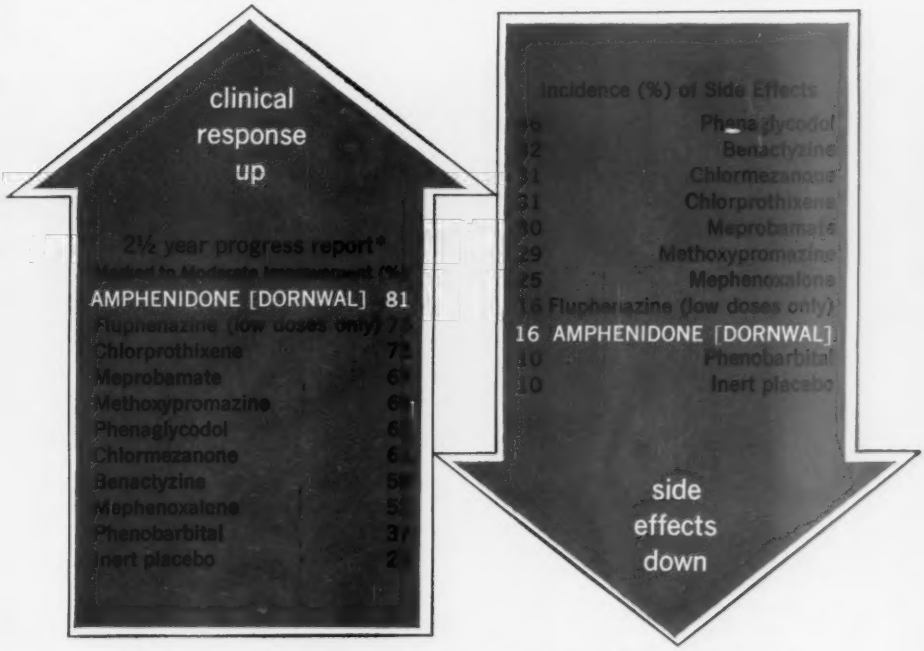

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*Nodine, J. H.; Bodi, T.; Slap, J.; Levy, H. A., and Siegler, P. E.: Human bioassay of tranquilizers in psychosomatic disorders, Scientific Exhibit, American Medical Association Annual Meeting, Miami Beach, Florida, June 13-17, 1960.

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1. Stephens, V. C., *et al.*: J. Am. Pharm. A. (Scient. Ed.), *49*:620, 1960.
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